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BROMSULPHALEIN LIVER FUNCTION TEST IN SEVERE INFANTILE GASTROENTERITIS

EXPERIMENTAL STUDIES ON FUNCTIONAL CAPACITY OF THE LIVER IN INFANTS

BY

JYRKI KAUHTIO

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI AND
FROM THE CHILDREN'S CASTLE OF THE MANNERHEIM LEAGUE, HELSINKI.
CHIEF: PROFESSOR ARVO YLPPÖ, M.D.

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PREFACE

It is a pleasure to express my sincere gratitude to my revered teacher, Professor ARVO YLPPÖ, M.D., for his generous permission to perform my investigations in the institutions superintended by him. His sympathy, encouragement and guidance were of great value to me in the course of my work.

The subject of my investigation was suggested to me in 1948 by NIILO HALLMAN, M.D., Assistant Chief of the Children's Clinic, under whose guidance the research on infantile diarrhea has been performed at our hospital. He spared no pains in following the development of my work, gave valuable advice and generally assisted me in every way, for which I wish to express my deep gratitude.

I am also greatly indebted to Professor C.-E. RÄIHÄ, M.D., who has kindly read my paper and made valuable suggestions, and to E. K. AHVENAINEN, M.D., pathologist to our hospital, for placing at my disposal his post mortem material, and for his helpful criticism.

My very warm thanks are due to Miss HELVI KESKELÄ, R. N., whose zeal and great experience were of the utmost assistance to me in the performance of my experiments. My thanks are also due to other members of the staff for the help they gave me while my work was in progress.

The English translation of my study was done by Mrs. E. HARDEN and revised by my colleague A. LOXDALE, M. D., to whom I offer my sincere thanks.

Helsinki, May 1950.

The Author

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I. Introduction

In Finland, severe diarrhea plays a considerable part in infantile mortality (15—25 per cent) during the first year of life (YLPPÖ). Research work has therefore been in progress for some years at the Children's Clinic of the University of Helsinki, and it is hoped that its results will throw additional light on this problem. The present investigation is a link in this work and one of its details.

The extensive literature pertaining to infantile diarrhea has repeatedly drawn attention to the possible role of the liver in this disease. CZERNY (1897) and THIEMICH (1896) were probably the first to associate disturbed liver function with the pathogenesis of »toxicosis». Later FINKELSTEIN (1921), MARFAN (1923), SCHIFF and his coworkers (1922, 1924) and CANELLI (1930) have stressed this possibility, and recently MARIE (1947), LEVESQUE (1947), GORNITSKAYA (1947), SCHLESINGER (1949) and their collaborators have studied the question in connection with severe gastroenteritis. Yet the liver function in the course of this disease was very seldom studied by modern methods, and therefore an attempt to elucidate the problem in our clinical material seemed justified.

Among numerous so-called hepatic tests preference was given to the bromsulphalein test (ROSENTHAL & WHITE, 1925) regarded as comparatively reliable and sensitive. It was intended, by performing this test during different phases of the disease, to demonstrate possible disorders of liver function in patients suffering from severe infantile diarrhea, and to search for a possible correlation between the results and the phenomena characteristic of this disease.

To my knowledge, similar studies have not been published so far. Since these tests seem to have been only infrequently performed on infants, it was felt that an additional study of control material was necessary.

Before describing the results of my investigation, it seems appropriate to create a background for it. The following general survey of literature presents a short review of severe infantile diarrhea, the problem of fatty liver associated with it, and the studies concerning the bromsulphalein test.

II. Survey of Literature

Classification of Intestinal Disorders in Young Infants

The literature dealing with nutritional and intestinal disorders of young infants has, in the course of several decades, gained a prominent position in pediatric publications. This may to some extent be due to the circumstance, that only very few groups of children's diseases present greater difficulties with regard to etiology and pathogenesis than those generally classified as diarrheal disorders. In the course of time attempts have been made again and again in several countries to group and classify these disorders. It is not easy therefore to obtain a general idea, in consequence of the different outlooks and dissimilarities in terminology. Yet it appears evident that geographical, climatic and other factors play a considerable part, and a classification which appears natural and appropriate under certain circumstances, does not seem to gain recognition in another country, with different conditions. An extensive and contradictory literature consequently supplies most unsatisfactory data on causation and differentiation of primary and secondary intestinal disorders, which are further complicated by several potential pathogens localised in the alimentary tract and the uncertainty of their isolation.

While attempting to present below a short survey of the literature dealing with severe gastroenteritis, the author wishes to emphasise particularly that, with a view to simplifying matters, the terms gastroenteritis and toxicosis are used as general denominations, irrespective of the standpoint of the writer under discussion, as to their etiology e.g. It is evident that different etiological factors, both known and unknown are involved. These are often related

to each other and produce certain acute symptoms of which the most common are diarrhea and vomiting. This combination is contained in the diagnosis of acute gastroenteritis, according to the terminology in use at our hospital.

Infection and Gastroenteritis

The opinion that acute infantile gastroenteritis is most frequently induced by infection has of late been winning general recognition. In the light of our later knowledge concerning child welfare the purely alimentary diarrhea, previously regarded as important, is rapidly losing ground. With the improvement in hygienic conditions there is also a pronounced decrease in diseases caused by specific intestinal bacteria (Bloch, Lyon & Folsom, Siwe, Hinden, Lichtenstein, Fanconi, Adam, Rohmer etc.). On the other hand, some workers want to adopt an entirely new concept — »the epidemic diarrhea of the newborn», on which attention has been focused particularly on account of its high mortality rate, and whose virus etiology appears probable (Rice & al., Buddingh & Dodd, Light & Hodes, Cummings, Biering-Sörensen & al., Gerbeaux etc.). Yet viewpoints have been advanced, according to which this disease does not differ essentially from the diarrhea met with in older infants, and there shoud be consequently no reason to place it in a group by itself (Clifford, O'Keefe, Hinden).

It must be concluded, on the basis of negative stool cultures and a simultaneous manifestation, that bacterial and virus infections, producing so-called »colds» in adults and older children and occurring in our country over the greater part of the year, are related to infantile diarrhea (Ylppö). The fact is particularly stressed by Ylppö that the lungs and the digestive tract develop from the same embryonal organ, the coelenteron, and even if differentiation is completed in the early stages of fetal life, time is needed to attain local immunity. During the first months of life the intestinal, as well as the general power of resistance is poor, and therefore the identical infection which in adults is confined to symptoms of the upper respiratory tract, attacks as well, or solely, the intestine in infants (Evans, Alexander & Eiser, Jeans & Floyd, Smellie, Frant & Abramson, Campbell & Cunnigham, Hinden).

As far as conditions in our country are concerned, this can be said to apply in part to summertime infections, probably of enteral character, and evidently associated with the milk hygiene. As already mentioned owing to the power of resistance increasing with age, such infections in adults do not produce anything more serious than mild disorders of a few days' duration, but in infants an acute fatal gastroenteritis is frequently the outcome. Experience has shown that improper feeding of the infant and other disorders in its development are significant as predisposing factors, and also the great importance of constitution in the genesis of severe gastroenteritis should be emphasised. Attention has been directed to these factors in the past by CZERNY, and recently by FANCONI.

Toxicosis, intoxication, l'état toxique, coma dyspepticum

Particularly in the 1920:s and 30:s investigations were made on the syndrome of severe gastroenteritis, to which the terms toxicosis, intoxication, coma dyspepticum etc. are applied. Depending on different outlooks, the diagnosis is naturally the outcome of a subjective judgment, and only describes the severity of the disease (PARRISH). In the literature this term is mainly used for a certain catastrophe in basal metabolism, its essential features being dehydration, circulatory disorders, certain nervous symptoms, as well as symptoms produced by the respiration, the kidneys and the digestive tract. In the course of the last decades, investigators appear to have reached the unanimous conclusion, that toxicosis as such is a fully unspecific syndrome, particularly typical of young infants, which can be produced by certain etiological factors. It involves fundamental organic functions and a vicious circle is produced (MOON), where it is difficult to distinguish between causes and results. In the course of time this ring has been studied by investigators from different starting points, and they have subsequently attempted to throw light on the whole complex according to their point of view.

Viewpoints on the Genesis of the Toxic State

The high content of fluids in the infant organism as compared to that of the adult, as well as its high hydrolability (GAMBLE,

KERPEL-FRONIUS, ROMINGER, DARROW etc.) frequently revealed by infection, are well-known facts. Dehydration and the disastrous loss of weight induced by it are therefore essential phenomena in severe infantile gastroenteritis, to which attention had even been directed in the literature of last century.

The central role played by dehydration in the genesis of the toxic state associated with infantile gastroenteritis has been crystallised by MARRIOT into a so-called anhydremia theory, which has also been independently described by BESSAU under the heading of exsiccation; this theory was subsequently completed by him, and reference will be made to it later. Whatever the etiology of gastroenteritis, it leads according to MARRIOT to dehydration of the organism. As a result of it, the blood becomes concentrated and its amount in the circulation reduced, which affects intermediary metabolism and plays a large part in causing of acidosis. Anhydremia produces a condition which, according to MARRIOT, is largely comparable to hemorrhagic shock. He claims that anhydremia alone explains the condition of toxicosis, and he has experimentally demonstrated this on an idiot aged 5 months. However he does not deny the possible share of undefined toxins, but considers it unnecessary to advance such a hypothesis. Dehydration also causes lesions to body cells, which is manifested in prolonged athreptic states of infants who have recovered from the acute stage of severe gastroenteritis.

Even if anhydremia, on the basis of later research, has been relegated to a position of secondary importance as compared to general dehydration of the organism, the observations of MARRIOT and BESSAU have provided a foundation for an extensive literature dealing with the subject, which has thrown additional light on changes occurring in the water balance of the organism during severe gastroenteritis.

Since, however, the water equilibrium is essentially dependent on intracellular and extracellular electrolyte balance, research into these questions has greatly extended the range of our knowledge. The publication of KARL SCHMIDT dealing with cholera was several decades ahead of its time. Fifty years before the appearance of the dissociation theory of electrolytes he suggested that intracellular and extracellular fluids are different, and that the

organism does not only lose water during intestinal disturbances, but also certain cations.

To my knowledge, the next significant observation was made at the begin of the 20th century. STEINITZ found that diarrheal acidosis was associated with the loss of sodium and potassium. TOBLER and two years later JUNDELL measured this removal of electrolytes and observed typical changes in the mineral concentrations of the tissues. Mention can also be made, among European workers, of KERPEL-FRONIUS, BRATUSCH-MARRAIN, STOLTE and SECKEL. Therapy does not seem to have been greatly affected by these investigations; American workers were the first to put these as well as their own observations into practice (HOLT & al., SCHLOSS & STETSON, HAMILTON & al., HARTMANN, POWERS, KARELITZ & SCHICK, RAPOPORT & DODD etc.). A noteworthy feature of these and especially of later American researches is their general lack of any pronounced opinion on »toxicosis», which plays the principal role in contemporary European investigations. It appears, however, that the diagnosis »dehydration» in these papers often includes this conception.

The investigations of GAMBLE and collaborators which threw light on the distribution of fluids in the organism and the association of changes occurring in them with certain electrolytic disturbances were to some extent of fundamental importance. Furthermore, DARROW's numerous publications are worth mentioning, and their results have made it necessary to revise some erroneous opinions on the characteristics of the walls of living cells; his work has also had a decisive influence on modern gastroenteritis therapy.

European workers have not as a rule confined themselves to interpreting the state of intoxication associated with severe infantile gastroenteritis as being induced solely by dehydration and loss of minerals. Instead, more or less clearly defined toxic agents are often brought forward as additional, sometimes even as primary factors. CZERNY has definitely introduced the term »toxicosis», and he seems to be the first to have made a search for these substances in the intestinal contents, without result however. CZERNY's original theory implicated in the first instance some acid substances appearing in the intestine from food, which under pathological conditions pass direct into the blood and produce an »acid poisoning».

Certain theories concerning various acids had been advanced before him by FLEISCH, JAEGER and WALTER, and these were followed by investigations dealing with organic acidosis frequently manifested in association with severe gastroenteritis (STEINITZ, PFAUNDLER, MEYER & LANGSTEIN, YLPPÖ etc.). HOWLAND and MARRIOTT seem to have introduced into pediatrics the concept of »alkali reserve». Even if the factors inducing acidosis have been demonstrated by later investigations, yet the significance of the acidotic state for the development of the disease still needs further elucidation.

Wide recognition has been gained by FINKELSTEIN's theory on the genesis of toxicosis or »intoxication», as he expresses it. He drew attention to the fact established by LUTON and MARFAN in the last century, that an administration of food when the disease has reached its peak generally aggravates the condition. According to his original opinion, milk sugar injures the intestinal wall owing to intestinal fermentation, and the salt substances in whey are then directly transmitted as such into the intermediary metabolism, producing fever and typical toxic symptoms, extensively described by him in collaboration with MEYER. »Alimentary fever» is the cause of dehydration, involving in the first instance the liver and producing disturbances in intermediary metabolism as well as intestinal disorders.

The theories advanced by SCHIFF were also based on unspecified toxins and suggested that protein metabolism could run its normal course only if a sufficient amount of water was present. In dehydration toxic substances are generated partly in the bowels, and partly in the liver as a consequence of damage to it. The detoxicating capacity of the organism, above all the liver, is also disturbed by lack of water, and »shock toxins» then appearing pass freely into the circulation, producing the typical picture of the disease.

The so-called Coli-endotoxin theory named after BESSAU was only formed when BESSAU, without any knowledge of MARRIOT, connected it with his opinion on the significance of dehydration. The basis for this theory was the observation of the enormous spread and increase of coli bacteria in severe gastroenteritis (PLANTENGA, ADAM, MORO, BESSAU & BOSSERT, SCHEER, KRAMAR etc.). The experimental work of this school (ROSENBAUM, CATEL &

PALLASKE, CHASSEL, KELLER, LODENKÄMPER, STERN, MARTYN etc.) has demonstrated that in dehydration not only the permeability of the intestinal wall, but that of the brain capillaries is changed as well, and therefore coli-toxin is able to affect the nervous system. According to this, toxicosis is a complex of symptoms largely of a cerebral character which, in order to develop, need dehydration on the one hand, and the effect of endotoxin on the other. This point of view is based in the first instance on animal experiments, a circumstance which was criticised even by several of the authors themselves.

Taking as his starting point similar observations as those made by BESSAU, i.e. multiplication of coli bacteria and their invasion of the upper parts of the small intestine in severe infantile gastroenteritis, as well as the fact that coli bacteria break up certain amines in proteins, MORO developed a theory of his own on the genesis of the toxic aspect of the disease, which has gained wide recognition. The main idea of the so-called amine theory of MORO is that toxicosis is an enteral poisoning caused by products of disintegration from food proteins acted on by bacteria. This theory initiated a period of intensive research work (BOYD, RÖTHLER, MEYER & ROMINGER, BRANDES, PAFFRATH, KELLER, MALYOT, MELLANBY, BURCHARD, TILING, NUSSBAUM, LINNEWEH, DODD & al. etc.). On the one hand, successful attempts were made to bring about in different ways, using histamine and other amine compounds, a typical aspect of toxicosis while dehydration was present. On the other, substances could be demonstrated in the blood and the intestinal contents of toxic infants which affected the guinea-pig by increasing its intestinal tonus, or they caused a picture resembling histamine shock in exprimental animals. DIECKHOFF was even able to establish a correlation between the histamine and choline concentration of the blood and the course of the disease. However, all the investigators already mentioned are not unanimous as to whether these »shock toxins» are produced in the intestine, instead, the role of histamin generated in tissues by anoxia has been stressed (SCHIFF). EPP's observations also seem to belong to this group; he maintained that the activity of aminoxidase in hepatic and other tissues of infants is low and increases with age. BEST et al. and later GRAF have found that the histamine concentration of

the blood is heightened during anoxemia. STRÖDER has observed that the activity of acetylcholinesterase is unmistakably lower than normal during toxicosis.

In addition to amines generated by bacterial activity, so-called evaporating fatty acids have also been studied, and their abnormal manifestation has been made responsible by some workers for the causation of toxicosis (HEUBNER, SALGE, BAHRDT, EDELSTEIN, LANGSTEIN, WELCHE etc.). This opinion was overshadowed by the former several decades ago.

Parenteral infections have also been incriminated as the most fundamental cause of a certain group of gastroenteritis, in particular otitis media and so-called occult mastoiditis have been studied. In some publications they are considered specifically as causative agents of the toxic phase of the disease, whereas others confine themselves to stating that they frequently appear simultaneously with severe gastroenteritis (TRÖLTSCH, GOEPPERT, HARTMAN, PONFICK, HEERMANN, ALDEN, LYMAN, MARRIOT, JEANS & FLOYD, FRANT & ABRAMSON, JOHNSTON & al., JACCOTTET, GUNN & SMELLIE, GAIRDNER, WEISSE, VOLFKOVICH etc.). Some writers have drawn very far-reaching conclusions regarding therapy (ROHMER, RAMOS). Recently it was again demonstrated by STENGER in dogs that irritation of the middle ear can be significant in the causation of toxicosis.

Symptoms pertaining to the nervous system, essentially associated with toxicosis, have also been widely studied, as already indicated (BESSAU, ROSENBAUM etc.). Some investigators have found more or less pronounced anatomic changes in the brain and nervous tissues of infants who have died of toxicosis (ZAPPERT, THIEMICH, GOLDZIEHER, KRÀMAR & al., ECKSTEIN, GLOBUS & al). On the other hand, such changes could be brought about, with a certain measure of success, in experimental animals with artificially induced toxicosis (PLANTENGA, SCHAFERSTEIN & al.). Disorders in the function of the autonomic nervous system during toxicosis have focused attention in particular (BEREND, TEZNER, BOSCHAN, MOGWITZ, KRAMER, GRIMM, HEIM etc.). Thus the French school which considers lesions in the autonomic centres primary phenomena, and dehydration, diarrhea, circulatory disturbances etc., secondary ones, has attempted to explain the genesis of toxicosis from a new

angle (REILLY & al., RIBADEAU-DUMAS & al., ALAJOUANINE & al., MARQUEZY & LADET). This opinion has been supported by many others (BRATUSCH-MARRAIN, STENGER, PETERS & al. etc.), and it seems that the toxic aspect of the disease can very well be explained on this basis.

The foregoing short and necessarily incomplete survey provides some idea of the tremendous amount of work done with the purpose of studying infantile gastroenteritis and the toxic aspect of this disease, as well as the origin of these conditions. Even if these investigations have brought to light quite a number of facts, our knowledge on many essential points is still incomplete, and the interpretation of some observations a subject of controversy. Considering, in addition, that the material is most heterogeneous, one is not surprised at the controversies in some countries between different opinions expressed. Yet it appears that theories on the genesis of the toxic condition are now considered of secondary importance, research being in the first instance directed to exposing the changes occurring in the cells in the course of the disease, and to developing therapy, which has naturally brought about an improvement in the results.

»Fatty Liver«

It is well known that autopsies on cases of severe gastroenteritis frequently show few changes when compared to the dramatic course of the disease. Pediatric and pathological textbooks draw attention to this, and in addition to intestinal changes, they often mention fatty liver as a salient feature, even if they do not regard it as a typical phenomenon of this disease (MITCHELL & NELSON, PFAUNDLER & SCHLOSSMANN, HOLT, HENKE & LUBARSCH, MOORE).

During the last decades these changes had been repeatedly studied by several workers (THIEMICH, ROSENHAUPT, CZERNY, MARFAN, HUEBSCHMANN, SAITO, STEPHANI, ROSENBAUM, BONHAM-CARTER, SCHLESINGER & al., MARIE & al., HALLMAN & AHVENAINEN etc.), but their interpretations are still subject to controversy. Several of these authors regard the fatty changes as degenerative and a mark of liver

damage. On the other hand, theories have been advanced claiming that fatty metamorphosis of the liver, at least in its mildest stages, does not produce demonstrable functional disturbances (CZERNY & KELLER, HANSER, HIMSWORTH etc.), but is a physiological phenomenon at a certain digestive phase (HOLMGREN, MÖLLERSTRÖM). In addition to fatty changes of different degrees of severity ,the livers of infants succumbed to severe gastroenteritis have revealed enlargement of the capillaries, accumulation of hemosiderin (SAITO, DUBOIS, STEPHANI), and different bacteria (CZERNY). Miliary necroses have also been found (SCHNEIDER, SCHWARTZ, KONSCHEGG, BONHAM-CARTER), as well as early fibrosis (SCHLESINGER & al.). The different findings reported by various investigators evidently arise from the time elapsed between death and autopsy, in addition to dissimilarities in the disease itself.

The role of the liver in the metabolism of fats is more or less obscure, but it is considered evident that the main part of fats passes through it, either to be stored or used up according to requirement. At this stage considerable amounts of phospholipids are needed and produced (BEST). All those factors which interfere with their formation, produce an accumulation of fat in the liver (PETERS & VAN SLYKE, ABDERHALDEN & MOURIQUAND). Since varying amounts of fat appear in hepatic cells under normal conditions (FISCHER, HERXHEIMER, FRANK & STOLTE, FORSGREN), it is difficult to draw the line of demarcation in regard to pathological fatty metamorphosis. Opinions have been advanced even in the course of the last century that fatty liver is not pathological in itself, instead, it is a mark of the function of this organ, either under normal or pathological conditions (HELLY, HIMSWORTH, KÖLLIKER, LEYDIG). It has been particularty stressed that post mortem it is difficult to differentiate between a functionally normal cell and a damaged one (THIEMICH, HANSER, v. GIERKE, DIETRICH, AHVENAINEN). In so far this is possible among other things on the basis of nuclear changes, one can speak of proper fatty degeneration (VIRCHOW).

Fatty metamorphosis of the liver in infants affected with severe gastroenteritis is generally regarded as due to the deleterious influence of bacterial or other toxins (THIEMICH, CZERNY & KELLER, HUEBSCHMANN, SAITO etc.). Dehydration has also been held responsible

for fatty metamorphosis (ROSENBAUM, STEPHANI). LEVESQUE & al. incriminate viruses, MARIE & al., SCHLESINGER & al. and VÈGHELYI seek the basic cause in a deficiency of so-called lipotropic factors.

There does not seem to be at present a generally recognised basis of interpretation as to when the fat revealed in hepatic cells of infants, who have died of severe gastroenteritis, is to be considered due to the physiological function of the cells, and when it has accumulated in the cells as a result of damage. On the other hand, it is generally recognised that this fatty metamorphosis is of the nature of infiltration and not degenerative in the majority of cases (ROSENBAUM, HANSER, HIMSWORTH etc.).

Experimental research has also attempted to throw some light on the question of fatty liver. It is known that during fasting glycogen and protein decrease in the liver and are replaced by fat (ADDIS & al., KOSTERLITZ & al.). It was also demonstrated in diarrhea patients that fat replaces glycogen in the liver (ROSENFELD, ROSENBAUM). It has been well known for a long time, that fatty changes of the liver can be brought about by certain organic and inorganic toxins. Recent studies have also demonstrated that fatty liver results from a diet rich in fats, the removal of the pancreas (BEST & al., DEUEL & al.), as well as during deficiency of some so-called lipotropic factors in the diet. BEST and HUNTSMAN have demonstrated the lipotropic effect of choline, TUCKER and ECKSTEIN found methionine to possess the same influence. Du VIGNEAUD has claimed on this basis that fatty liver occurs on a diet deficient in labile methyl groups necessary for choline synthesis. CHAIKOFF and ENTENMAN found that there is a disturbance in the mechanism removing methionine from protein for lipotropic purposes.

DRAGSTEDT and collaborators have reported another factor, lipocaic formed in the pancreas, supposed to be a proteolytic enzyme, but CHAIKOFF and coworkes were able to demonstrate in it a non-proteolytic component as well. Lipotropic characteristics have been found, apart from choline, in some vitamins of group B, in pyridoxine (HALLIDAY, SCUDI & HAMLIN) and pantothenic acid (ENGEL). Attempts have been made to apply these observations in therapy, but so far results seem to be doubtful (ELGOOD, LEVESQUE & al., SCHLESINGER & al., MENEGHELLO). On the other hand it could be demonstrated that at the peak of severe gastroenteritis,

there is a diminished secretion of the pancreatic enzyme, as precursor of the manifestation of fatty liver (VÈGHELYI).

It is evident on the basis of the foregoing that several prerequisites of fatty metamorphosis of the liver, as revealed by experimental studies, are in existence under conditions produced by severe gastroenteritis. Yet the mechanism of fatty metamorphosis still remains to be exposed finally and conclusively.

Bromsulphalein Liver Function Test

An extensive literature shows that during the last decades repeated attempts were made in different countries to develop a test which could be used as an indicator of the functional capacity of the liver (BAUER 1906, van den BERGH & SNAPPER 1913, STRAUSS 1922, ROSENTHAL & WHITE 1925, BERGMANN & ELBOTT 1927, QUICK 1932, EPSTEIN 1932, WATSON 1936, KOLLER 1936, POLLAK 1937, MALLOY & EVELYN 1937, HANGER 1938, LOEB 1941, LORD & ANDRUS 1941, GRAY 1942, POST & PATEK 1943, MACLAGAN 1944, etc.).

Howewer, great difficulties have had to be overcome, due to the following factors consistently described by several investigators:

1. Our knowledge of the numerous functions of the liver as well of the factors regulating them is largely inadequate.

2. In pathological conditions all known hepatic functions are not disturbed simultaneously or to a similar degree.

3. The liver is a highly dynamic organ, and its functional capacity varies.

4. The reserve power of the liver and its regeneratory capacity are extensive.

It is evident, even on this basis, that in order to gain reliable knowledge by modern methods, different parallel tests must be performed and repeated at set intervals. In addition, the value of hepatic tests depends on their proper interpretation in relation to the history, physical findings, the stage and course of the disease, the results of other diagnostic procedures, and the presence of other conditions which might influence the results. When properly selected, performed and interpreted, hepatic tests are capable of providing information that is of great assistance in the diagnosis,

prognosis and management of patients with suspected or established liver disease (PARKER, BOLLMAN & MANN, MATEER & al., STEIGMANN & POPPER, OSGOOD, DUCCI, IVY & ROTH, ODIN, WATSON etc.).

A detailed description of these various tests appears superfluous in this connection. It is sufficient to state that the majority of them are still under development. With the progress of research work, it has become evident that the results of many such tests are dependent on other factors as well, in addition to the function proper of parenchymal hepatic cells. Quite a number of so-called liver function tests have been abandoned in the course of time, after it was found that their results were not particularly associated with hepatic cells.

Opinions as to the superiority of one test or another, their specificity and sensitivity have also varied and are probably still varying. The subject of this work, the bromsulphalein test has maintained its position for a quarter of a century. In spite of being non-physiological, it has been recognised as one of the most sensitive and reliable among liver function tests, and it often reveals parenchymal liver damage in non-icteritic patients at an early stage (SNELL & MAGATH, MATEER & al., OSGOOD, STEIGMANN & POPPER, etc.).

The bromsulphalein test (BSP test) was introduced for clinical use in 1925 by ROSENTHAL and WHITE. Even before that some phtalein derivates injected had been found to be excreted apparently into the bile, and the conclusion was drawn that this phenomenon could be used as a quantitative liver function test (ROWNTREE & al., WHIPPLE & al., DAWSON & al.). A step forward was the observation of ROSENTHAL in 1922, that the amount of these dyes remaining in the blood was correlated with their excretion into the bile. Extensive investigations performed on experimental animals (ROSENTHAL & WHITE) showed that bromsulphalein (phenoltetrabromphtalein-disodiumsulphonate) synthetised by WHITE in 1918 had properties best suited for the purpose. (Fig. 1.) It was excreted into the bile to the extent of 60—90 per cent within one to two hours after intravenous injection. It could not be demonstrated in the urine, unless considerable amounts were injected. It did not seem to possess any untoward effects. By ligaturing the hepatic blood vessels of experimental animals it was noted that

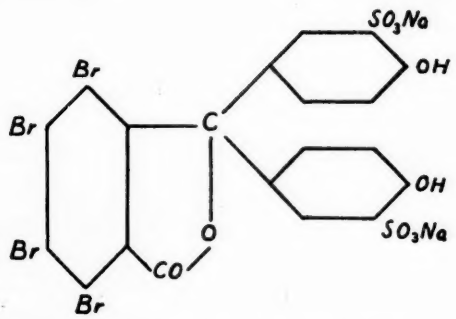

Fig. 1. — Chemical structure of Bromsulphalein indicator dye (phenoltetrabromphtalein-disodiumsulphonate).

the retention of the dye in the blood was in relation to the quantity of liver parenchyma, whose function was thus disturbed.

ROSENTHAL made a suggestion as to the mechanism of this test which is still generally recognised in its main features. In his opinion, the BSP, as well as some other colour substances (rose bengal, bilirubin) is bound in the blood to the plasma protein, which explains why it is not normally excreted into the urine. In the liver this »adsorption unit» is split up under the influence of bile salts, and the dye passes into hepatic cells which excrete it into the bile. In his dialysis experiments performed in vitro, ROSENTHAL conclusively proved the effect of bile salts (taurocholate) on the removal of the dye from proteins. The same results were later obtained by BRADLEY et al. and BRÁUER and PESSOTTI; the latter were able to establish in addition that the dye is attached to the plasma albumin fraction.

The BSP test was rapidly adopted for general clinical use and, as already mentioned, it is still considered one of the most sensitive indicators of the functional capacity of the liver. Similarly to all so-called liver function tests, this one has also been severely criticised. HERLITZ was apparently the first to maintain that the elimination of BSP from the blood was not a function of hepatic cells, but produced by the reticulo-endothelial system (RES), largely through the action of the KUPFFER cells. Later on KLEIN and LEWINSON performed animal experiments with this object in view, taking as their starting point the observation that the RES generally removes colloidal dyestuffs from the blood circulation (ASCHOFF,

RIBBERT, GOLDMANN & KIYONO). They blocked the RES in dogs by India ink injections and obtained, in subsequently performed BSP tests, results different from normal. Similar experiments have also been performed by MILLS and DRAGSTEDT, and the results of all indicate that RES cells play a considerable part in the elimination of BSP from the blood. COHN et al. have studied the disappearance of BSP from the circulation of normal and eviscerated dogs, and they stress the share of extrahepatic tissues in the elimination of the dye. On an average they were able to collect from the bile less than 50 per cent of the amount of the dye injected, whereas the results generally attained were 60 to 100 per cent (ROSENTHAL, CANTAROW).

CANTAROW and WIRTS have studied in detail the excretion of BSP into the bile. They directed attention to the fact that the injected BSP disappears from serum almost completely within 15 to 45 minutes, whereas the excretion into the bile can proceed for several hours. It is evident under these circumstances that two different mechanisms are involved. The removal of the dye from the blood stream is largely the result of the function of KUPFFER cells in the RES. Its excretion into the bile on the other hand, is supposed to be brought about by the function of parenchymal hepatic cells. Later investigators all agree with a practically similar view; e.g. LAVERS et al., who particularly emphasise that if the function of parenchymal cells is poor, the RES is blocked by the dyestuff and is powerless to eliminate it from the blood. Thus a retention different from the normal occurs, which is reduced according to the capacity of hepatic cells to excrete the dye into the bile. HERLITZ, attempting to explain retentions different from normal, observed by him in association with some bacterial diseases, believes that the RES is blocked by bacteria and their toxins. Whereas WIRTS Jr and BRADFORD were able to demonstrate that the excretion of BSP into the bile can be greatly delayed, even if its elimination from the blood is normal, they consider this as a mark of functional disorders in parenchymal cells.

It has long been wellknown that cardiac insufficiency and hepatic disorders are associated with each other. It is in fact evident that the BSP retention in the blood depends, in addition to function of liver parenchyma, on cardiac circulatory factors (JOLLIFFE,

Robertson & al., Bernstein & al., Cantarow, Boland & Willius, Chavez & al. etc.). It is a common observation in the studies dealing with these questions that in compensated cardiac insufficiency the BSP retention is as a rule normal. In uncompensated hearts retention values exceeding normal have often been found, but no mathematical correlation could be established between the degree of severity of the heart lesion and the extent of the retention of the dye. Blumberg and Schloss examined patients who had both cardiac failure and some liver disease. They came to the conclusion, that a BSP retention different from normal in these cases is due both to disturbed excretory capacity of the liver, and to circulatory disorders. If one of these factors was subjected to changes, this was generally revealed in the BSP tests, even if it was still impossible to establish any mathematical correlation.

Räihä considers it probable that the secretory capacity of the glands is related e.g. to the amount of blood passing through them. It is therefore impossible, without a determination of the hepatic blood flow, to make a reliable distinction between the functional disorder of the liver, due to local circulatory factors and revealed in the elimination and excretion of the BSP, and disorders produced by an altered activity of parenchymal cells. To give a proof of the intimate correlation between local circulatory factors and cellular changes in the liver, it seems appropriate to mention the investigations of Glynn and Himsworth. It is well known that a strong fatty degeneration of the liver can be induced by carbon tetrachloride. These investigators were able to demonstrate that respiration of this vapour in the rat immediately causes a considerable constriction of hepatic sinusoids for several hours, with an ensuing pronounced ischemia of the liver. Some hours later the hepatic cells reveal vacuolisation and other degenerative changes, which these writers ascribe to anoxia. Similar observations have been made by Wakim and Mann, and with chloroform by Loeffler and Nordmann. It is also known that general anoxia caused by other means produces changes in hepatic cells (Trowell, Rich). It could be shown, on the other hand, that after anesthesia with chloroform and ether, the BSP test is different from normal (Rosenthal & Bourne). Furthermore, it was observed that an administration of oxygen protects the liver from the effects of carbon tetrachloride and of

chloroform (GLYNN & HIMSWORTH, GOLDSCHMIDT & al.). On this basis, it appears evident that local circulatory factors and anoxia due to them, can play a considerable part in »functional disorders of the liver», by causing damage to parenchymal cells. To some extent their influence is also evident in experimentally established functional disorders, regarded as primary changes in the activity of parenchymal cells.

Determinations of the hepatic blood flow have in fact been performed under normal conditions using BSP and assuming that its normal elimination from the blood is a mark of the activity of the liver, and that it is brought about by other means only to an insignificant extent (GRINDLAY & al., BRADLEY & al., MYERS). It has also been assumed that the BSP dye used in these tests does not in itself increase the hepatic blood flow, although some other dyestuffs are known to have that effect (WAKIM).

Experimental animals have been found to exhibit BSP retentions different from normal in association with severe fatty changes of the liver induced by carbon tetrachloride, phosphorus and dietetic means (HOUGH & FREEMAN, FASHENA, BEST). If smaller changes occurred, BSP tests were generally normal (CHENG-FA WANG & al., MACLEAN & al.). Yet it is difficult to decide, as far as these investigations are concerned, whether a functional disorder of hepatic cells alone is involved, due to their fatty metamorphosis, or whether a disturbed hepatic blood flow is also concerned in this phenomenon.

It must be said moreover, that HICKS et al. have performed BSP tests during arteficial hyperpyrexia, and observed in the course of these experiments that variations in the retention found in individual patients were in correlation with the rise and fall of the temperature. Since it was difficult to assume in these cases that there could be any question of a reduced hepatic blood flow, these authorities came to the conclusion that a heightened BSP retention is a manifestation of a functional disorder in the parenchymal cells of the liver. Similar observations were made in connection with malaria (MACHELLA). Yet there are some investigations which could not establish any correlation to the rise in temperature (FRIEDERICKS & HOFFBAUER, KOPP & SOLOMON, KEYS & al.).

HARRIS has performed liver function tests on 30 cases of pneumococcus pneumonia using e.g. the BSP test, and as controls patients

uffering from scarlet fever, erysipelas, tonsillitis and pulmonary tuberculosis. According to him, the results indicate that the liver function is more impaired in pneumonia than in some other types of infectious diseases and that fever alone is not responsible for the liver damage. He suggests also that if the disturbances of function encountered in pneumonia are due to circulating toxins, these toxins have a more specific affinity for the liver than in other diseases studied.

STILES and collaborators have published a study of patients with low-grade chronic illness, in which chronic infection appeared to play an important part, and simultaneously BSP tests differing from the normal were found in several cases. These workers mention in addition that liver dysfunction has been reported associated with a variety of chronic or recurrent conditions; e.g. allergy, arthritis, peptic ulcer, glaucoma, Parkinsonism, thyrotoxicosis, rheumatic fever, various infections and bacterial intoxications.

References to studies of BSP tests performed on infants are very scarce in the literature. HERLITZ published in 1927 a series of 38 cases, in which he found the BSP test suitable for use on young children as well. In 1925 ABALLI and CASTELLANOS made similar tests with phenoltetrachlorphtalein, which was abandoned later, and BOSSERT and LOERS performed tests in 1924 with methylene blue and indigo carmine. In 1927 LEVIN carried out BSP tests on a mixed series and obtained positive results in some cases. WATERLOW, reporting in 1948 a certain fatty liver disease in infants in the British West Indies found positive BSP tests in these patients as a mark of impairment in liver function. The BSP excretion in the newborn was studied, in addition to HERLITZ, also by SALMON and RICHMAN (1943), MOLLISON and CUTBUSH (1949), as well as by YUDKIN and collaborators (1949). It could be demonstrated that the elimination of the dye was slower than in adults, and that it improved during the first days of life.

In the course of time, the BSP test was modified in different ways. ROSENTHAL's original dose was 2 mg of the dye per kilogram of body weight. MATEER et al. showed that the test is made more sensitive by administering a dose of 5 mg/kg. There were also variations with regard to the time of withdrawal of the samples (ROSENTHAL, MATEER & al., MACDONALD), even if 30 minutes were

considered as most suitable in the 2 mg, and 45 minutes in the 5 mg test. It is evident that for clinical use, a visual comparator method is sufficient. MATEER et al. regard it as normal in doses of 5 mg/kg, when the dye is completely removed within 45 minutes, although some other investigators tolerate a retention up to 0,4 mg %. If the more sensitive photoelectric method is used, a slight retention should still be considered normal in the 45 minutes test. In order to avoid errors of interpretation in connection with the dosage of the dye and the different methods used, some investigators have recurred to BSP clearances estimated in different ways (CHENG-FA WANG & al., MCKIBBIN & al., MACLEAN & al.). LAVERS and coworkers have reported a sensitive modification of the BSP test, in which the elimination of the dye from the serum is determined at definite intervals, and the result is registered numerically as clearance coefficient.

Liver Function Tests in Infantile Gastroenteritis

Although impairment in the liver function has been repeatedly described as highly significant in the literature pertaining to severe infantile gastroenteritis, references to liver function tests performed on such patients are scarce. This is probably due in the main to those difficulties which are associated with examinations of the liver function, and to which reference has already been made.

PFAUNDLER (1901) and BRÜNING (1903) have demonstrated in vitro with salicyl aldehyde that the oxidating capacity of the liver was decreased in infants succumbed to toxicosis. HELLER (1923) and TAKEDA (1928) have felt justified in concluding, on the basis of the so-called »Hämoklasische Krise», that the liver function of these patients is impaired, whereas BROWN (1928) came to the opposite result, by using levulose tests as well. Different sugar tolerance tests have been advocated by GOETZKY (1920), HECHT and NOBEL (1922), DUZAR and HENSCH (1924), TAMURA (1939), as well as GAVRILOW (1940). In their experimental exsiccation studies, SCHIFF and coworkers (1924), using the bile test (»Gallenprobe», FALTA & al.), came to the conclusion of a disturbed function of the liver.

Bossert and Loers (1925) subjected 20 diarrhea patients to tests with methylene blue (Rosental & Falkenhausen) and indigo carmine (Lepehne), recovering the excreted dye with a duodenal sound. In the majority of cases the excretion differed from the normal, and the authors formed the opinion that this was due to lesion of the liver cells. Recht's (1935) study of the Takata reaction makes reference to some toxicosis patients, and likewise Hirsch (1939) has obtained positive results in some cases.

Marie and collaborators (1947) mention determinations of the prothrombin time, cholinesterase and esterified serum cholesterol, as well as thymol tests, but no actual results are reported in their studies.

Petryaeva (1947) has performed Takata-Ara tests and determined plasma cholesterol in prolonged infantile dysentery obtaining positive results.

Schlesinger and coworkers (1949) have determined the prothrombin time and plasma bilirubin for some patients, and mention alkaline phosphatase determinations and thymol turbidity tests.

Prothrombin time was also studied by Widenbauer and Krebs (1942), Plum (1943), Rapoport and Dodd (1946), as well as Hallman and Kauhtio (1949); these latter have systematically performed vitamin K tests on their patients and obtained in some cases results differing from the normal.

It appears therefore that liver function tests in severe infantile gastroenteritis have been performed very infrequently, and partly by methods whose reliability, according to modern opinion, is questionable.

III. Present Investigation

Method

In the present investigation a 5 per cent Bromsulphalein standard solution (HYNSON, WESTCOTT and DUNNING, INC., BALTIMORE) was used and diluted immediately before the test to 1 per cent by adding saline, in order to increase the volumes to be handled. The dosage remained constant throughout, i.e. 5 mg of the dye per kilogram of body weight, or 0,5 ccm/kg of the foregoing solution. The infusion technique was that generally used in our hospital. A needle of medium size (No. 2) was inserted into one of the scalp veins, saline was injected in order to check that the needle had entered the lumen of the vessel, and the dye was injected over a period of about 1 minute using a short connecting tube. The syringe was then filled three times with the saline solution, which was injected in the same way in order to rinse the tube. These infusions were not found to have produced complications in any single instance.

The blood specimens were withdrawn from the superior sagittal sinus by using a larger needle (No. 1) and a fresh syringe, care being taken to avoid hemolysis. No complications could be observed in connection with the 500 sinus punctures which were carried out in the process of this investigation. After clotting had occurred, the samples were centrifuged in the usual way. The serum was withdrawn by means of pipetting, centrifuged again and removed, after which it was diluted with saline to 1:2 or 1:4. The specimens could then stand at least 12 hours without altering.

Estimations of the bromsulphalein retention were performed from serum dilutions with COLEMAN Universal Spectrophotometer (wavelength 580 mμ) and in part with LEITZ's photoelectric colorimeter (filter D). Control determinations which were carried out simultaneously gave practically identical results, in consequence of which the apparatus mentioned above were sometimes interchanged if required. The difference in double determinations did not exceed 0.05 mg %. For this reason some of the later determinations were carried out once only.

To eliminate possible hemolysis, an acidified serum dilution (one drop 10 per cent HCl) was used in some determinations as standard solution, by means of which the photometer could be adjusted to zero. After this the reading of the alkalised specimen (one drop 20 per cent NaOH) was made. Simultaneously, a corresponding serum dilution without any addition of acid was used as a comparison solution. The differences in the results of these determinations were found to be insignificant when clear serum was used.

With a view to reducing the amout of blood needed for the experiment, it was decided to adopt this latter procedure only, and the majority of determinations were performed in accordance with it. Thus, the serum dilution 1:4 was used first to adjust the photometer reading to zero, was then alkalised by adding one drop of a 20 per cent NaOH solution, after which the characteristic bluish purple colour of bromsulphalein became visible, and the result was read from the scale of the photometer.

A calibration curve was prepared in the early stages of the work by testing known saline and serum saline dilutions of the dye, and it was then observed that the standard error was 0.02 mg %. The BSP concentration of the samples was then obtained in the actual tests in mg% from this curve.

Before the performance of the BSP tests the infants had to fast for 6 to 8 hours, during which only sugar water was given. This was done to avoid lipemia of the serum. Only clear serum was used for the estimations, and hemolysed specimens were disregarded, even if this is not considered absolutely necessary (GAEBLER). No systematic determinations of the icteric indices of the samples were performed, but icteritic serum did not occur in these experiments. Alterations in the optical density of clear control serum dilutions by adding alkali were found to be insignificant.

A. Experiments on Healthy Infants

1. Elimination of BSP from the Blood Stream

With a view to obtaining a reliable control material, studies were made on the disappearance of BSP from the serum of healthy infants whose age ranged from 2 weeks to 12 months, with no history of previous liver disorders and no clinical signs of them. Tests were performed on 30 infants from whom samples were taken at different intervals after the injection of the dye. The results are tabulated below.

Table 1. Elimination of BSP in healthy infants

Interval after injection (min.)	10′	15′	30′	45′	120′
Number of determinations.....	15	15	15	15	10
Retention in serum (mg %) ...	2.0±0.2 *	1.2±0.2	0.3±0.05	0.2±0.02	0.1±0.02

* *The mean error of the mean value has been calculated on the basis of the usual formula* $\varepsilon\,(M) = \sqrt{\frac{\Sigma \Delta x^2}{n\,(n-1)}}$

The results show that most of the dye is removed from the blood within a few minutes after the injection, and that in 10 minutes only 11—26 per cent of the amount injected can be demonstrated in the serum by the method used. In 45 minutes no dye can be detected, practically speaking, in the majority of cases. The retention continues to fall within 120 minutes in those cases where the elimination was not complete in 45 minutes. Individual variations were considerable.

The excretion of the dye into the bile was not examined, in consequence of the complicated methods required for it.

2. BSP Tests in Healthy Infants

The normal BSP test (5 mg/kg dye, specimen in 45 min.) was performed on 56 healthy infants whose age varied from 2 weeks to 12 months, and of whom 23 were boys and 33 girls. Four infants were subjected to the test 2 to 3 times. The retention varied in both sexes, being on an average 0.21 mg % in boys and 0.25 mg% in girls. The average age of the boys in this series was about 4.8 months and of the girls about 3.7 months. If the results are grouped according to the age of the infants, the following table is obtained.

Table 2. Retention in BSP tests of healthy infants

Age of infants	0 < 1 months	1 < 3 months	3 < 6 months	6 < 12 months
Number of cases	6	20	20	10
BSP retention (mg %)	0.38	0.28	0.16	0.12
Limits	0.3—0.4	0.1—0.4	0.0—0.4	0.0—0.2

In spite of considerable individual variations, the table illustrates the tendency to a lower retention with increase in the age, and this phenomenon also explains the difference in retention observed in both sexes.

3. BSP Tests and Day Rhythm of the Liver

In order to elucidate whether the rhythmic function of the liver is manifested in the elimination of BSP, i.e. whether the time of day has any effect on the result of the BSP test, it was performed on four healthy infants three times in the course of one day. Immediately after each experiment the babies were given their usual food. The results are shown on the table below.

Table 3. Retention in repeated BSP tests

Time of the day	10 p.m.	6 a.m.	2 p.m.
Case 1. 2 months	0.3 mg%	0.2 mg%	0.2 mg%
Case 2. 3 »	0.1 »	0.3 »	0.2 »
Case 3. 4 »	0.3 »	0.4 »	0.4 »
Case 4. 5 »	0.2 »	0.3 »	0.3 »

By withdrawing the blood specimen before a fresh injection of the dye it was observed that none of the cases revealed any retention from the previous injection. No noteworthy difference was seen in the results of tests performed at different times of the day.

4. BSP Clearance Coefficient

A more sensitive modification of the BSP test was recently described by LAVERS et al., based on the rate of disappearance of the dye within a definite interval of time. They recommend 20—30 minutes after the injection as a suitable interval. Numerically this elimination of the dye is expressed as clearance coefficient.

$$\text{Clearance coefficient} = \frac{\log_e (B_1) - \log_e (B_2)}{t_2 - t_1}$$

B_1 being the BSP concentration in the serum at the moment of withdrawing the first sample (t_1) and B_2 the concentration at the moment of the second withdrawal (t_2). In the study referred to above the normal limit of the clearance coefficient was found to be 0.08—0.03 in adults, on the basis of 80 cases examined. Values

below 0.03 are considered an absolute mark of an inadequate liver function.

In this study the clearance coefficient was calculated for 24 healthy infants, with an age varying from 1 to 12 months. The following table sets out the results.

Table 4. BSP clearance coefficient in healthy infants

Time of withdrawal of sample	Number of cases	Average value	Limits
10' and 30'	4	0.0475	0.054—0.041
15' and 45'	12	0.0294	0.061—0.016
20' and 30'	4	0.0152	0.035—0.006
30' and 45'	4	0.0281	0.066—0.006

The values of the coefficient, low throughout, are a striking feature. Their common average is 0.03, i.e. the identical figure which is given in the foregoing study as the absolute normal limit for adults.

If these results are grouped according to the age of the infants, the following table is obtained.

Table 5. BSP clearance coefficient in various age groups

Age of infants	1<3 months	3<6 months	6<12 months
Number of cases	8	9	7
Average.....	0.027	0.030	0.036
Limits	0.054—0.006	0.061—0.006	0.066—0.010

This table shows that there are no noteworthy differences between different age groups. Yet the average value of the coefficient seems to show a rising tendency with the increase of age, although the results are not conclusive mathematically.

Discussion

The results obtained are consistent with those of earlier studies (MATEER & al., etc.). The elimination of the BSP from the blood stream seems to proceed by two stages (CANTAROW & WIRTS). The first was found to occur rapidly, within a few minutes in both animal experiments and in adults, as well as in the newborn (MOLLISON & CUTBUSH). During this stage from 30 to 80 per cent of the dye injected is removed from the blood stream. In my own investigation the elimination of the dye during the first 10 minutes was found to occur on an average in 80 per cent. Infants of different age did not reveal any noteworthy divergencies in this respect, but individual variations were considerable.

The second stage of the elimination ends in healthy adults within 30—45 minutes after the injection; after this interval there is, practically speaking, no retention of the dye (MATEER & al., CANTAROW & WIRTS etc.). It was found that the second stage is slower in the newborn than in adults, and retention was detected in the serum several hours after the injection of the dye (MOLLISON & CUTBUSH). The identical phenomenon could be observed in this investigation, with a retention of 0.1—0.2 mg % in some healthy infants as late as 2 hours after the injection of the dye.

The conception of two different mechanisms in the elimination of BSP from the blood stream seems to be generally recognised (CANTAROW & WIRTS, MILLS & DRAGSTEDT, LAVERS & al. etc.). According to it, the first, rapid stage of elimination is due to the RES, in the first instance, to the function of the KUPFFER cells. The second, slower stage, during which the dye is being excreted into the bile, is ascribed to the function of the parenchymal cells of the liver. Under these circumstances it becomes evident that a BSP retention differing from the normal can be due either to the blocking or immaturity of the RES (HERLITZ, KLEIN & LEVINSON, MILLS & DRAGSTEDT), or to excretory insufficiency of the liver (YLPPÖ, WEECH, MOLLISON & CUTBUSH, YUDKIN & al.), whatever the cause of the latter, or to the simultaneous effect of these factors.

In order to throw additional light on this question I have performed animal experiments, which are still in progress. In frozen sections prepared from the liver of test animals the dye seemed to be

demonstrable both in the RES as well as in parenchymal hepatic cells. This observation supports the earlier views regarding the double mechanism of the BSP test.

HERLITZ came to the conclusion in his experiments that BSP elimination from the blood is deficient in infants up to 4—5 months of age, being largely due to the poor development of the RES. The poor capacity of elimination in the newborn has been demonstrated by MOLLISON and CUTBUSH who found, similarly to HERLITZ, that there was no correlation to the severity of jaundice. ABALLI and CASTELLANOS found that the phenoltetrachlorphtalein retention decreased during the first days of life in the experiments performed by them. Likewise YUDKIN et al. obtained lower values of BSP retention in babies a few days old than in the newborn, and they consider that circulatory insufficiency of the newborn is one of the possible causes. Their series did not reveal any correlation between the birth weight and the degree of retention. It is evident that circulatory factors, above all the hepatic blood flow (BRADLEY & al.) play a considerable part, direct or indirect, in the appearance of BSP retentions different from the normal, as could be demonstrated by BLUMBERG and SCHLOSS, in addition to some authors already mentioned.

My own series also shows a growing tendency to a lower retention with advancing age.

It was also found by the authors already referred to that the BSP retention in the 45 minutes' tests was higher in their infant series than in adults. The paper published by SALMON and RICHMAN describing that they did not, using comparator estimations, find any retention in the newborn, conclusively proves the effect of the method on the results.

The day rhythm characteristic of the liver could be experimentally demonstrated (FORSGREN, HOLMGREN, MÖLLERSTRÖM). It appears probable, on the basis of a small test series, which was only meant to serve a definite purpose, that the results of BSP tests in infants are not dependent on any possible day rhythm.

LAVERS et al. who have published a study dealing with the BSP clearance coefficient, obtained considerable differences between normal adults and those suffering from hepatic lesions. By withdrawing blood specimens in 20 and 30 minutes after the injection

of the dye, they found that the coefficient value 0.03 was the absolute line of demarcation between a normally functioning and an injured hepatic parenchyma. In my own study, 24 infants known to be healthy had this same average value of 0.03 for the BSP clearance coefficient, and a considerable number of the results lay above that threshold. This seems to be mainly due to the reduced rate in the second stage of the elimination. In my test series the BSP clearance and consequently also the clearance coefficient were naturally higher at longer intervals (10—30 or 15—45 minutes) than in the shorter period suggested by LAVERS (20—30 minutes). Individual variations were considerable. Even if the results are handled in this way, they indicate that the excretory capacity of the liver with regard to BSP, i.e. its functional capacity in a certain respect, is smaller in infants than in adults and appears to grow with increasing age. Similar inferences were drawn by YUDKIN et al., who found some other simultaneously performed, so-called liver function tests (thymol turbidity and flocculation, cephalin-cholesterol flocculation and colloidal gold test) to be normal, and advanced the opinion that the BSP retention demonstrated was not due to lesions of the hepatic parenchyma, but to immaturity of the liver typical of the newborn (YLPPÖ, WEECH).

Conclusions

1. In BSP tests (5 mg/kg, specimen in 45 minutes) performed by the method described a retention of 0.0—0.4 mg% must be considered normal in infants aged from 2 weeks to 12 months.

2. The time of day does not seem to affect the results of the BSP tests.

3. The results of the BSP tests are not affected by a test performed 8 hours before, the retention having entirely disappeared in the meantime.

4. The elimination of BSP from the blood is unmistakably slower in infants than in adults, and seems to increase with age.

B. Experiments on Gastroenteritis Patients

Material

The series comprises 50 cases who all had a serious prognosis and were treated at the hospital in 1949. 7 patients came from the same orphanage which in the course of the year had twice been affected with a restricted epidemic of diarrhea, 6 infants had fallen ill in some other institution, and the remainder at home. There were 27 boys and 23 girls. Seven were prematures of whom three died. 33 patients were discharged as recoveries (66 per cent), the number of those who died thus being 17 (34 per cent). If the material is grouped according to sex, the following table is obtained:

Table 6. Distribution of the material

Sex	Number of cases	Recovered	Died
Males.....	27 (54 %)	19 (70 %)	8 (30 %)
Females.....	23 (46 %)	14 (60 %)	9 (40 %)
Total	50	33 (66 %)	17 (34 %)

The material can in this respect be regarded as fairly homogeneous. No noteworthy differences between the sexes are detectable, instead, the dissimilar percentages are probably due in the first place to the scarcity of material.

When grouping the series according to the age of the patients, it is seen that there were 7 (14 per cent) under 1 month of age, 21 (42 per cent) $1 < 3$ months, 14 (28 per cent) $3 < 6$ months and 8 (16 per cent) $6 < 12$ months old infants. The age was calculated on admission. Their fate is illustrated by the following table:

Table 7. Mortality in different age groups

Age of patients	$0 < 1$ months	$1 < 3$ months	$3 < 6$ months	$6 < 12$ months
Number of cases.....	7	21	14	8
Died.....	4 (57%)	4 (19%)	6 (43%)	3 (37%)

Variations in the death rate shown by the table must be ascribed to the scarcity of the material as their chief cause. On the other hand, it was affected by the dissimilarity of the disease itself. To name an example, in the group of infants aged $1 < 3$ months »intoxication» was added to the diagnosis in 14 cases only (67 per cent), and the mortality rate was 19 per cent, whereas those $3 < 6$ months old were all deeply intoxicated, with a mortality rate of 43 per cent. As well known, gastroenteritis is most fatal during the first month of life, which is also suggested by this series.

Complications

According to the histories taken, 16 cases exhibited prior to admission symptoms of the upper respiratory tract, such as cough and rhinitis, immediately associated with diarrhea and vomiting. In addition, other members of the family had had similar symptoms when the infant was affected with diarrhea in 8 cases. Intestinal disorders had been manifested in older members of the family in 4 cases. On admission, 10 patients had respiratory symptoms associated with diarrhea, and in the course of the treatment they appeared in another 10. Pneumonia was found in 6 babies, and 3 of them died, evidently of terminal pneumonia. The remainder of the patients in this series did not reveal pulmonary changes, either radiologically or at autopsy. Otitis media suppurativa was only detected in two cases who both recovered.

Thus, complications immediately associated with diarrhea appeared in all in 26 patients (52 per cent). Of them 21 (80 per cent) were exceedingly severe cases (»intoxication»), and only 5 died (20 per cent). Viewpoints have been expressed (HINDEN etc.), according to which gastroenteritis has a better prognosis in cases who are affected with complications (»parenteral diarrhea»). The results of this series give similar indications, even if it is too small for drawing any definite conclusions.

Furthermore, it is worth mentioning that 4 cases of this series were affected with hypertrophic stenosis of the pylorus (cases 5, 12, 16 and 36), and 1 with congenital stenosis of duodenum (case 49) who did nor survive. The pylorus was operated on in 3 cases and cleared up, the fourth died of pneumonia before operation. They had all come to hospital as gastroenteritis patients, and the foregoing findings were made after the acute stage was over.

Two patients (cases 13 and 33) had received penicillin treatment for congenital syphilis and were free of symptoms on admission. Both recovered from their gastroenteritis.

Two patients had eczema infantum of long duration (cases 19 and 40). The later died of pneumonia.

One of the patients in this series (case 37) had congenital heart disease (Ductus Botalli persistens) and died.

Treatment and routine examinations

The patients were treated according to the scheme generally used in our hospital. Their fluid balance was studied by routine determinations of he-

moglobin, hematocrit, plasma protein, chloride, alkali reserve, non-protein nitrogen and glucose. In addition, the blood picture, prothrombin time, plasma sodium, potassium and calcium were determined in the course of the disease, and spinal fluid examined whenever it was deemed necessary. Bacterial cultures from liquor and blood, as well as examinations of feces for pathogenic bacteria (typhoid, paratyphoid, dysenteria) gave negative results. Determinations of the blood group and Rh were made for every patient. The WASSERMANN reaction was negative without exception. In the initial stages of the disease, some patients revealed organic acids or small amounts of albumin in the urine.

Shock manifested in several cases was generally controlled immediately on admission by plasma or blood infusions, which were also used in the course of treatment to counteract and control anemia and the loss of protein. With this latter objective in view, casein hydrolysate was given in some cases, intravenously or per os.

Of the patients 44 were acidotic on admission. Acidosis was generally treated with every precaution, by parenteral administrations of 1.3 per cent sodium bicarbonate or sodium lactate 1.87 per cent, varying from 5 to 20 ccm/kg. Some cases exhibited temporarily, in the course of the treatment, alkali reserve values surpassing the normal. In addition to the methods already mentioned, loss of fluid was also controlled by 0,9 per cent saline solution, generally as HARTMANN's solution, as well as a 5 to 10 per cent glucose solution. It was at first attempted to replace the loss of potassium by giving DARROW's solution by the mouth, but for the later patients in this series DARROW's solution was introduced subcutaneously 60 ccm/kg daily, with simultaneous systematic determinations of the plasma potassium. The calcium balance was controlled by parenteral or peroral doses of calcium gluconate or calcium chloride.

Depending on the clinical picture of the disease, the patients were initially given either the whole amount of fluid parenterally by means of intravenous infusions and hypodermoclyses, or only sugar water and possibly DARROW's solution per os. In 1 to 3 days small doses of breast milk were also introduced and daily increased, if justified by the general condition of patients. The purpose was to introduce in the initial stages of the disease a daily parenteral and oral fluid amount totalling about 200 ccm/kg. In the subsequent stages the patients were put on a diet suitable to their age, and breast-milk was in some cases replaced by mare's milk.

In order to overcome infection, the patients were given, with three exceptions, penicillin i.m., depending on their weight, 20—40.000 units 2 to 4 times daily for varying periods. 38 patients also received streptomycin, depending on their weight, 20—80.000 units twice daily per os or i.m., generally only for a few days. In addition, some patients were also given sulpha drugs, and in some exceptional cases aureomycin and chloromycetin were administered according to the dosage generally in use. Ascorbin and the vitamin B complex were frequently given, and vitamin K introduced

parenterally when necessary. In some cases vitamin A and liver preparations were given and, equally when necessary, massive doses of vitamin D. Furthermore, four patients were given Percorten (desoxycorticosterone acetate) and another four lipocaic.

Duration of treatment

The average duration of treatment was 46 days for those 33 patients who recovered, without any noteworthy difference between the toxic and non-toxic infants. A time of treatment considerably shorter than normal was observed in those 3<6 months old, i.e. 29 days, and considerably longer than normal in those 6<12 months of age, i.e. 62 days. In all probability, this was largely due to dissimilarity in the character of the disease. According to time of treatment, the patients were divided as follows.

Table 8. Duration of treatment of recovered patients

Age of patients months	2—4 weeks	5—8 weeks	9—12 weeks
0< 1	—	2	1
1< 3	7	8	2
3< 6	7	1	—
6<12	—	2	3
Total	14	13	6

As already mentioned, 17 patients in this series died, two of them a few hours after admission, and 10 patients in all within the first two weeks of residence in hospital. The remaining 7 deaths were distributed over the following weeks, as illustrated by the classification according to agegroups:

Table 9. Duration of treatment in fatal cases

Age of patients months	0—1 weeks	1—2 weeks	3—5 weeks	6—9 weeks
0< 1	1	1	1	1
1< 3	1	1	1	1
3< 6	1	3	2	—
6<12	—	2	—	1
Total	3	7	4	3

1. Elimination of BSP from the Blood Stream.

The disappearance of BSP from the serum was studied in 20 diarrhea patients in different stages of the disease, for some of them repeatedly. The customary dosage of 5 mg/kg BSP was used, and the samples withdrawn at definite intervals after the injection. Results:

Table 19. Elimination of BSP in gastroenteritis patients

Interval after injection (min.)	10′	15′	30′	45′	120′	180′
Number of determinations ...	10	10	10	10	8	7
Retention in serum (mg %)	2.6±0.6	1.8±0.3	1.1±0.3	0.9±0.1	0.5±0.03	0.4±0.01

The results show that the tendency of the dye to disappear is similar to that of healthy infants, but its elimination from the blood stream occurs much slower than in the healthy. Even 5 hours after the injection the dye was clearly demonstrable in some cases by the method used. (Fig. 2).

It should be added that in 4 patients with a high BSP retention (1,7—2,2 mg% in the routine 45' test) no dye could be detected in the serum 24 hours after the injection. In tests performed immediately afterwards the retention was again considerable (1,1—1,7 mg%).

The BSP test was performed on 5 patients twice in the course of one day. Results:

Table 11. Retention in repeated BSP tests

Time of the day	1 p.m.	7 p.m.
Case 1. 2 months	0,3 mg%	1,0 mg%
Case 2. 4 »	0,1 »	0,1 »
Case 3. 4 »	0,9 »	1,0 »
Case 4. 3 »	1,2 »	3,5 »
Case 5. 2 »	1,7 »	1,5 »

In two cases the retention was clearly higher in later tests.

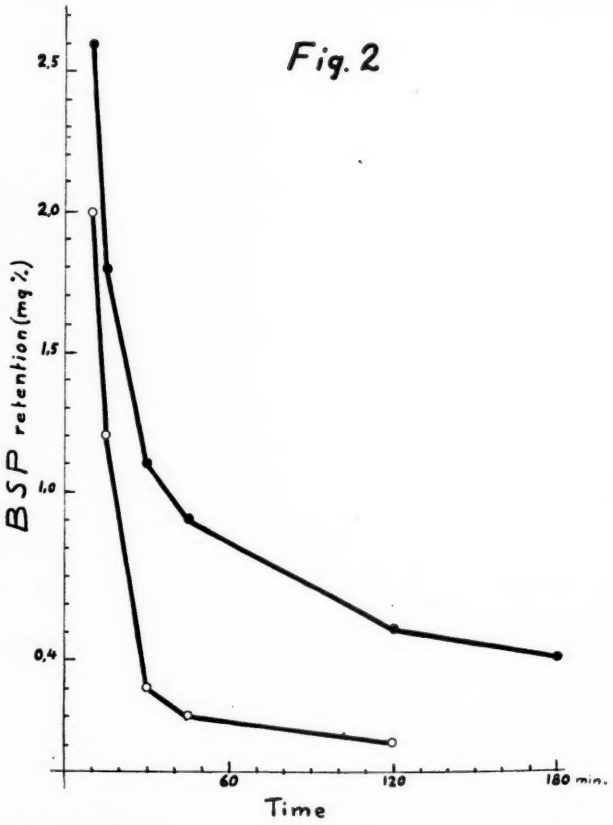

Fig. 2. — Disappearance of BSP from the blood stream in healthy infants (lower curve) and in gastroenteritis patients (upper curve).

2. BSP Clearance Coefficient

The clearance coefficient was calculated for 25 patients in this series, and the results are tabulated below:

Table 12. BSP clearance coefficient in gastroenteritis patients

Time of withdrawal of sample	Number of cases	Average value	Limits
10' and 45'	6	0.023	0.025—0.014
20' and 30'	13	0.012	0.047—0.000
30' and 45'	6	0.005	0.008—0.000

The coefficient values obtained are low throughout, and their common average is 0.013, or only half of the average in coefficients of healthy infants in this series.

When grouping these patients according to their age, the following table is obtained:

Table 13. BSP clearance coefficient in various age groups

Age of patients	0 < 3 months	3 < 6 months	6 < 12 months
Number of cases	14	8	1
Average	0.012	0.016	0.024
Limits	0.025—0.000	0.047—0.000	—

This table illustrates a tendency to a higher coefficient with increasing age, similarly to what can be observed in healthy infants. This becomes still more evident, if the three patients under 1 month of age are separated from the group of babies under 3 months old, the former having an average coefficient of only 0.004. Yet individual variations are so considerable that the result is mathematically inconclusive.

3. BSP Tests Performed on Gastroenteritis Series

a. HIGHEST RETENTION IN BSP TESTS IN DIFFERENT GROUPS OF PATIENTS

The patients of this series were subjected to the first BSP test generally within the first few days of treatment. It was performed in all about 350 times. The highest number of tests for one patient was 15, and less for those whose residence in hospital was shorter. In 10 cases the specimens were simultaneously withdrawn from the superior sagittal sinus and the external jugular vein or the cubital vein; it was revealed that the BSP concentration was then practically identical (deviation < 0.05 mg %).

The BSP retention was interpreted as follows:

0 — 0.4 mg %	normal retention
0.5 — 1.0 mg %	slightly increased retention
1.1 — 2.0 mg %	moderately increased retention
> 2.0 mg %	strongly increased retention

Recoveries

In 29 of those 33 patients who recovered the results of the BSP tests were different from normal at some stage of the disease. If the patients are divided on the basis of the foregoing classification according to their age groups, the following table is obtained:

Table 14. Highest retention in BSP tests on recovered patients

Age months	0—0.4 mg %	0.5—1.0 mg %	1.1—2.0 mg %	> 2.0 mg %
0 < 1	—	2	1	—
1 < 3	2	8	4	3
3 < 6	2	2	3	1
6 < 12	—	3	2	—
Total	4	15	10	4

The table shows that the retention remained normal in 4 patients, a slightly increased retention was seen in 15, a moderate in 10 and a strongly increased retention in 4 patients in the course of the disease.

Fatal cases

All the 17 patients who died had during the disease a BSP test differing from the normal, repeatedly as a rule. The height of the retention, with consideration of the patient's age, is illustrated by the following table:

Table 15. Highest retention in BSP tests in fatal cases

Age months	0.5—1.0 mg %	1.1—2.0 mg %	> 2.0 mg %
0 < 1	3	1	—
1 < 3	—	3	1
3 < 6	1	1	4
6 < 12	—	1	2
Total	4	6	7

A slightly increased retention occurred in 4 patients, a moderate increase in 6 and a strong increase in 7 patients. The ratio is therefore inverted, as compared to that of the recovered patients. (Fig. 3).

It seems evident that the height of the BSP retention has some correlation to the course of the disease, since stronger retentions are relatively more frequent in fatal cases. Proceeding from the assumption that the diagnosis of »intoxication» illustrates in a certain sense the severity of the disease, one also finds this correlation in existence, since patients for whom this diagnosis was established had also relatively more often higher BSP retentions than the non-toxic patients.

b. OCCURRENCE OF POSITIVE BSP TESTS DURING THE DISEASE

On the basis of the results of BSP tests performed in the course of the disease, the patients can be divided into different typical groups.

Recoveries

The first group embraces those 4 recovered patients in whom the BSP tests yielded normal results in all the stages of the disease. Case 1 was a case of pneumonia, associated with relatively mild diarrhea without acidosis and toxic symptoms. Cases 2 and 3 were typical cases of severe diarrhea who, on a parenteral potassium therapy, rapidly overcame their toxicosis and acidosis. Case 4 was only different in so far as he was affected with pneumonia as a complication.

The second group comprises 21 patients of whom 14 had BSP tests differing from normal only during the first week and 7 even during the second week of treatment. Fig. 4 shows the return of the BSP tests to normal in some typical cases. It can be found with regard to some patients of this group, that a BSP retention higher than normal is associated with high levels in erythrocytes, hemoglobin, hematocrit and plasma protein, indicative of dehydration. Frequently, however, the retention remains higher than normal while fluid therapy has been in progress already for a few days,

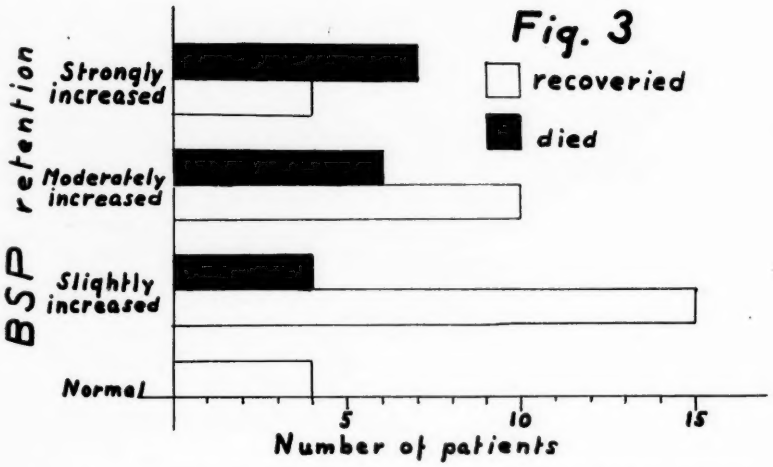

Fig. 3. — Distribution of the material according to the highest retention showed in BSP tests.

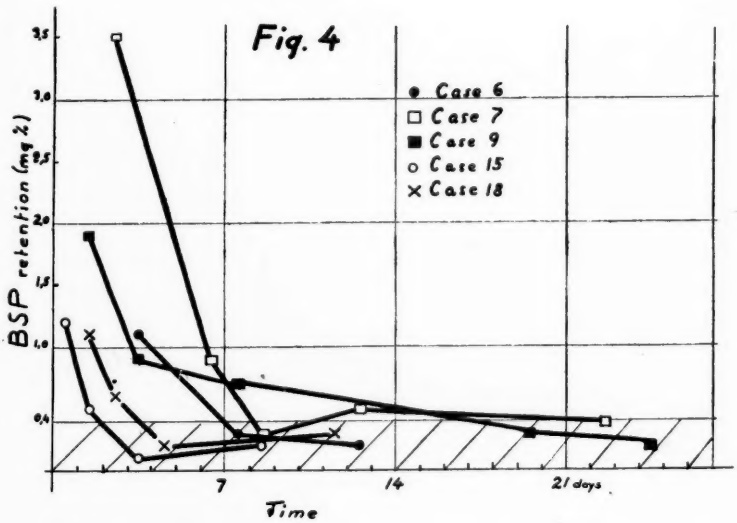

Fig. 4. — Rapid return to normal values in BSP tests of five typical cases.

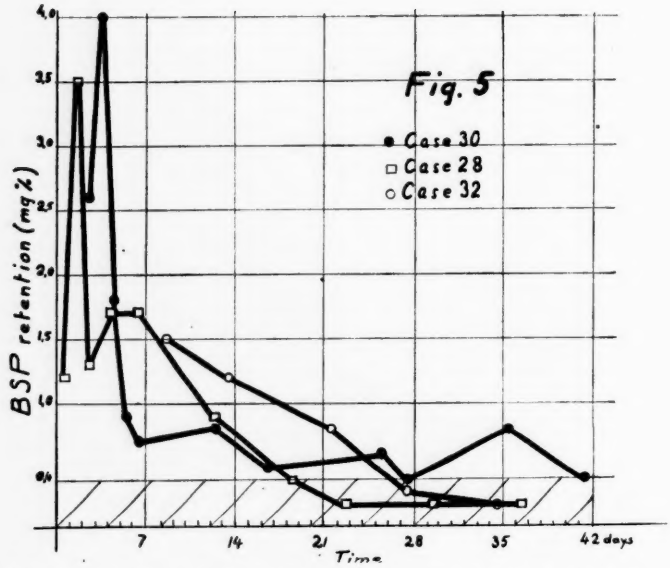

Fig. 5. — Slower return to normal values in BSP *tests of three typical cases.*

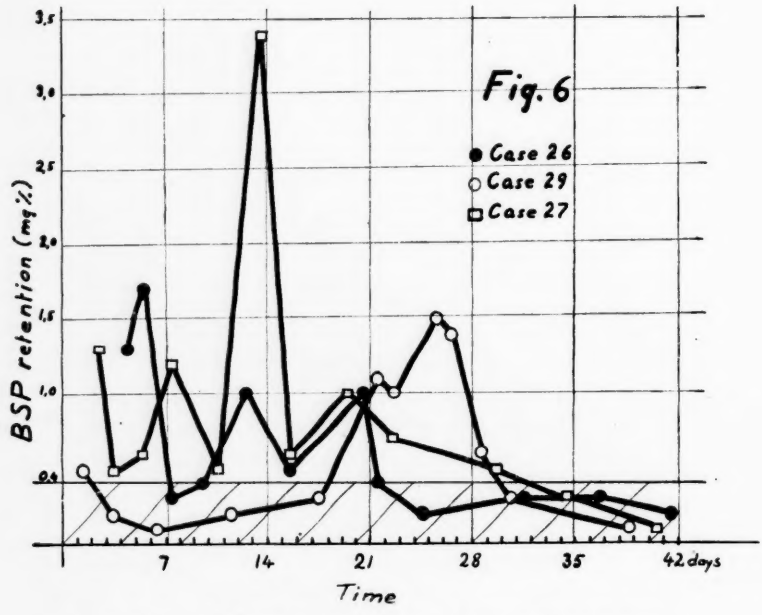

Fig. 6. — Changes in BSP tests of three prolonged cases.

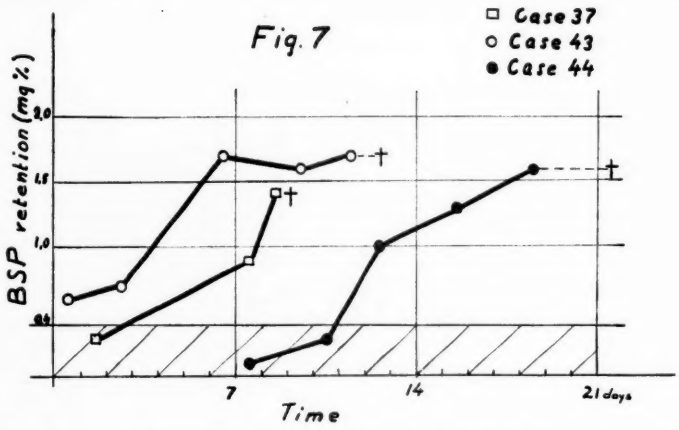

Fig. 7. — Increasing retention in BSP tests of three fatal cases.

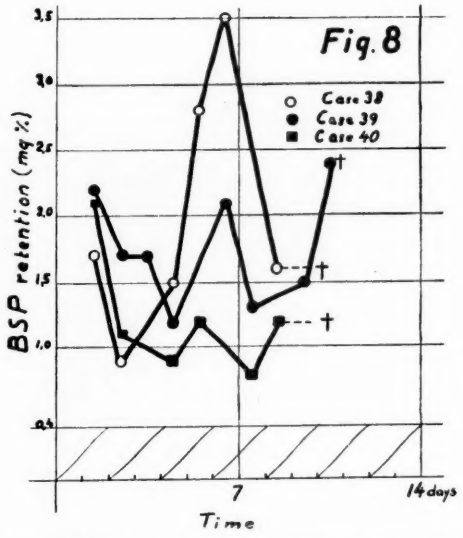

Fig. 8. — Changes in BSP tests of three acute fatal cases.

and these signs of anhydremia are not visible anymore. In some of the patients belonging to this group an enlarged liver was found which, however, quickly returned to normal.

The third group consists of 8 patients, in whom BSP tests differing from the normal were found during several weeks of treatment.

Fig. 5 illustrates the variations in BSP retention in three cases who revealed the highest retention in the initial stages of the disease, with a gradual return to normal of the results. In Fig. 6 three other cases can be seen, who had BSP tests differing from the normal for a duration of several weeks. The patients of this group seemed not to reveal any correlation to the hemoconcentration. They all had an unmistakably enlarged liver, which returned to normal under treatment, but in general only after the BSP test had gone back to normal.

It seems evident that a persistence of BSP tests differing from the normal in recovered patients is correlated with the general course of the disease, since the average duration of treatment was 39 days in the second group of patients, and 53 days in the third.

Fatal cases

Two of the patients in this series who died within a few hours from admission in a state of acidosis and circulatory collapse showed BSP tests differing from the normal. The remainder could be subjected to the BSP test for several times and yielded varying results. Fig. 7 illustrates three cases in whom retention grew from day to day as death approached. Fig. 8 presents three patients who died after a treatment of 9—11 days' duration and in whom the BSP retention varied but remained high in the course of the disease. Fig. 9 illustrates the variations in the results of the BSP tests performed on three patients whose disease ended fatally after several weeks' duration. Of these case 50 belongs to the same type as described in Fig. 7. Gross enlargement of the liver was found in all whose disease was of long duration. In order to make the picture more complete, Fig. 10 presents three patients whose disease ended fatally, but whose results in the BSP tests were different from those already described.

4. BSP Retention and the Size of the Liver

Some investigators have focused attention on enlargement of the liver frequently found in severe infantile gastroenteritis, and have even in part established their prognosis according to that

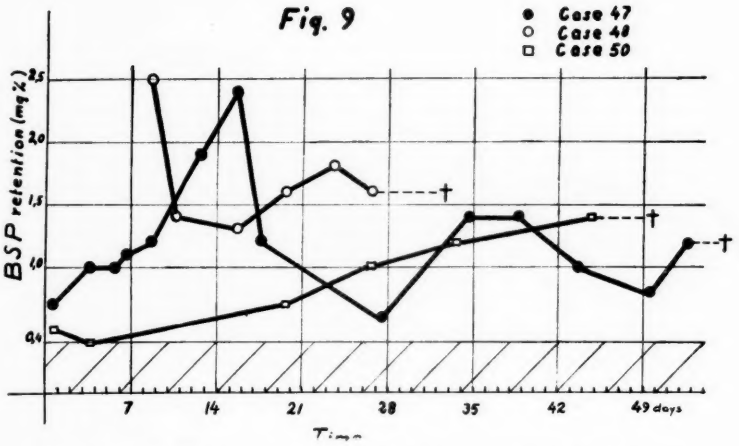

Fig. 9. — Changes in BSP tests of three prolonged fatal cases.

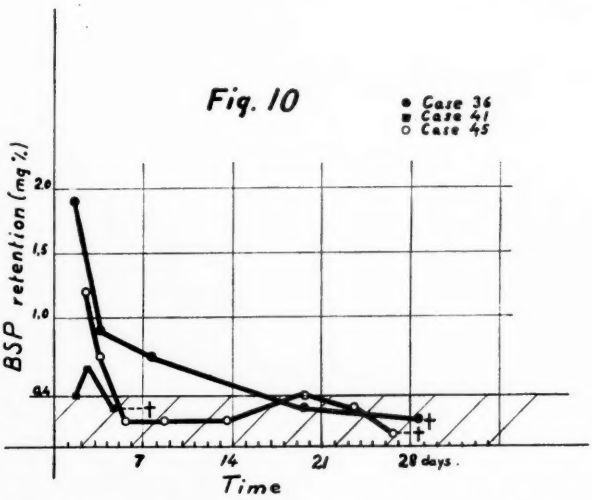

Fig. 10. — Exceptional return to normal values in BSP tests of three fatal cases.

phenomenon (GAVRILOW, SZÁSZ, MARIE & al., SCHLESINGER & al. etc.). The size of the liver was also observed in this series and measured in fingerbreadths below the costal margin, changes being recorded only when they could be recognised as certain. A liver palpable at one finger's breadth was registered as normal.

Several patients developed an enlarged liver with various velocity and without any detectable correlation to dehydration, duration and depth of acidosis etc. In some cases the liver attained enormous dimensions and was palpable as filling the main part of the abdominal cavity. There were 3 such patients (cases 26, 27 and 32) among the recoveries and 4 among those who died (cases 44, 47, 48 and 50).

The liver size was assessed in connection with 167 BSP tests in all and the enlargement classified as follows:

Group I = normal liver (the liver edge palpable maximum 1 fb below right costal margin)
Group II = liver enlarged (the liver edge palpable 2 fbs)
Group III = liver strongly enlarged (palpable 3 fbs, often filling the entire right iliac fossa and a considerable part of the left)

The determinations performed are tabulated below.

Table 16.

Liver size	Group I	Group II	Group III
Determinations in all	75	70	22
Determinations in positive BSP tests	47	59	18
Determinations in fatal cases.....	23	26	14

Fig. 11 illustrates the occurrence of the BSP retention revealed by the tests as compared to the size of the liver. It can be seen that all degrees of BSP retention were found while the liver was both normal and enlarged. Even if, in some individual patients, a BSP test different from the normal is frequently associated with an enlarged liver, it does not signify that this enlargement invariably involved BSP tests differing from the normal.

Autopsies were performed in 14 cases, which revealed that the enlargement of the liver was evidently due to fatty changes. In 7 cases the liver was transformed almost troughout into fat, five had less pronounced changes infrequently associated with congestion, either in the lobular periphery or in the central cells. In some cases

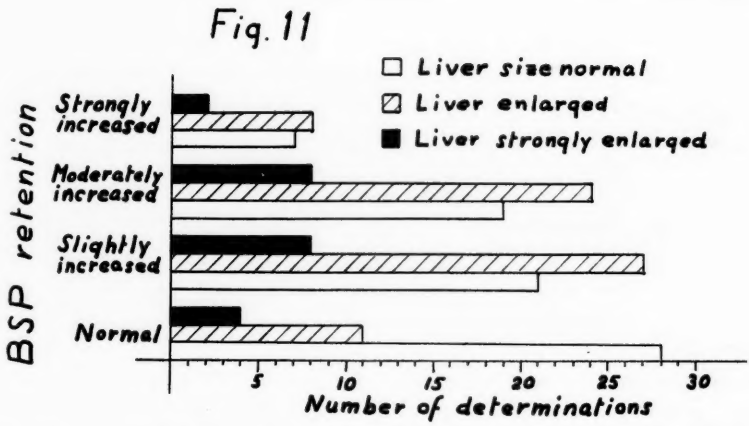

Fig. 11. — *Distribution of simultaneous determinations of BSP retention and the liver size.*

hemosiderin masses were found in hepatic capillaries. In two cases the autopsy did not reveal any fatty changes (Cases 36 and 45). Both were admitted in a state of malnutrition. In the literature opinions differ greatly as to the effect of nutrition on the fatty metamorphosis of the liver in gastroenteritis (CZERNY, ROSENBAUM, STEPHANI, LEVÉSQUE & al.). HALLMAN and AHVENAINEN came to the conclusion that fatty liver is more pronounced in patients who were well nourished before the onset of illness, which is also supported by this series.

5. BSP Retention and Prothrombin Time

Viewpoints have been expressed that a prolonged prothrombin time and a tendency to hemorrhages often associated with it in infants affected with severe gastroenteritis is a mark of disturbed liver function (MARIE & al., SCHLESINGER & al.). We have been able to demonstrate in an other connection by means of vitamin K tests (HALLMAN & KAUHTIO) that intestinal disorders as such are sufficient to explain this phenomenon.

In this series as well a prolonged prothrombin time (method of LEHMANN & QUICK) was found in several patients when the disease had been in progress for some time. 39 patients exhibited hemorrhage symptoms at some stage of the disease, and were given then, if not

before, 8—24 mg vitamin K soluble in water parenterally. They generally reacted to it by a rapid and pronounced increase of the prothrombin index. There did not seem to exist any correlation between the prothrombin time as such and the height of the BSP retention, as was to be expected on the basis of the foregoing exposition.

Yet the series comprises 22 patients in whom the reaction to vitamin K was different from the normal. Twelve of them recovered, six of whom had high BSP retentions and five were treated longer than average. Of the 17 fatal cases 6 gave an unmistakably negative and 2 a probably negative reaction to vitamin K, but the patients died before the control; another 2 had a delayed reaction. Seven patients were not examined. Results of BSP tests differed strongly from the normal, with the exception of 2 cases. Of them case 45 was a premature infant whose BSP test had been different from normal 3 times within the first week of treatment, but afterwards returned to normal values (Fig. 10). The vitamin K reaction was negative during the second and fourth week of treatment and the patient died in a state of atrophy in 4 weeks. Case 41 was admitted in a state of postacidotic atrophy. The BSP test was only once slightly different from the normal but the reaction to vitamin K failed, and the patient died on the eighth day of residence in hospital.

It appears that patients whose vitamin K test was delayed or wholly negative, generally had BSP values most differing from the normal, and that a negative vitamin K test presaged a fatal outcome.

6. BSP Retention and Temperature

On the basis of the investigations described above and concerning BSP retention during hyperpyrexia (HICKS & al., KEYS & al.), it was felt that a comparison between the results of BSP tests in this material and the patients' temperature would be justified. A total of 46 patients had BSP tests differing from the normal, and 47 patients exhibited a rise in temperature (38—41° C) at some stage of the disease, for causes which need not be discussed in this connection. In 11 patients the BSP tests were positive only while the fever lasted, in the remaining 35 also while the temperature was

normal. On the other hand, a normal BSP test was found in 9 patients simultaneously with high fever. Eight fatal cases had BSP tests which all differed from the normal; one of them ran a temperature during the whole time, the other 7 only now and then.

Under these circumstances, it cannot be denied that in some cases a rise in temperature might be connected with the appearance of positive BSP tests. On the other hand, no correlation can be demonstrated in this material between temperature and the degree of BSP retention; moreover, it appears to be of secondary importance in the majority of cases.

7. BSP Retention and Blood Chemistry

Hemoconcentration

An essential feature in severe infantile gastroenteritis is the appearance of hemoconcentration (MARRIOT, SECKEL, KERPEL-FRONIUS etc.). Particularly at the time of admission this phenomenon was also found in the patients of this series, simultaneously with BSP tests differing from the normal. It is, however, difficult to asses anhydremia, since one cannot exclude the possibility of anemia and hypoproteinemia before onset of the disease. In addition, the blood retains its normal concentration for a fairly long time even in dehydration, at the cost of the extracellular fluid (GAMBLE). After rehydration, the patients frequently reveal low values in hemoglobin, erythrocytes, hematocrit and plasma proteins, but it is evident that the disease itself also exercises its influence in that direction. Furthermore, as plasma and blood infusions were daily administered to the patients, the determinations performed do not give a true picture of the condition. However, the BSP retention has been compared with the results of the red blood count and plasma protein determinations.

Simultaneously, determinations of the hemoglobin level and the BSP retention were performed 95 times on the patients in this series, with the following results:

Table 17. Hemoglobin (%)

BSP retention (mg %)	> 85	85—65	< 64
0 — 0.4	7	18	5
0.5 — 1.0	10	16	9
1.1 — 2.0	7	12	4
> 2.0	1	5	1
Total	25	51	19

The normal hemoglobin values for infants reported in the literature vary considerably. MITCHELL—NELSON postulate 10.5—12.5 g % as a normal level during the first year of life, KUGELMASS 13.2 g %. WINTROBE has suggested 11.8 g % as an average during the first year of life, while VAHLQUIST, on the basis of Swedish material, mentions 12.0 g % (10.2—13.8) at the age of 3 months, and the identical 12.0 g % (9.8—14.2) at one year. Since the hemometer at our hospital (HELLIGE) states that Hb. 100 % correspond to 15,4 g % hemoglobin, I have regarded the values 70—85 as being normal levels in my series. The foregoing results demonstrate however, that BSP retentions of different degrees appeared both while the hemoglobin levels were normal, as well as above and below it.

Nor is hematocrit a reliable indicator of hemoconcentration, since it is known that the volume of red cells varies in the course of the disease (KUGELMASS, PRADER & ROSSI). WINTROBE gave the average value for this age as 35.5. In my series 32—40 were considered normal on the basis of experience. It was shown by 74 simultaneously performed determinations that the patients of this series revealed every degree of BSP retention, both while hematocrit was on a normal level, as well as below and above it.

The normal erythrocyte values reported in the literature for infants vary also: MITCHELL—NELSON state 4.3—4.7 mill./cmm, KUGELMASS 4.4 mill./cmm, FINDLAY 4.0—4.5 mill./cmm. VAHLQUIST obtained the average value of 4.2 mill./cmm (3.6—4.8) at the age of 3 months and 4.6 mill./cmm (3.8—5.4) at one year. As far as we are concerned, the averages appear somewhat high, but assessing on the basis of experience, the normal level of the Finnish

material is about 3.7—4.6 mill./cmm. Higher values are uncommon except in newborns. 92 simultaneous red blood counts and determinations of the BSP retention were performed on the patients of this series. The results were as follows:

Table 18. Erythrocytes (mill./cmm)

BSP retention (mg %)	> 4.6	4.6—3.7	3.6—2.5
0 — 0.4	7	11	9
0.5 — 1.0	8	17	11
1.1 — 2.0	12	6	4
> 2.0	2	3	2
Total	29	37	26

The table shows that all degrees of BSP retention were associated both with normal erythrocyte values, and those above and below the normal.

The plasma protein concentration is also generally regarded as an indicator of hemoconcentration, even if its increase is not in direct proportion to the severity of anhydremia (DARROW & BUCKMAN, KERPEL—FRONIUS, LINNEWEH, DIECKHOFF, SCHNEEGANS). In my material 114 simultaneous determinations of total plasma proteins (VAN SLYKE) and BSP retention were performed. It was found that low protein values were strikingly abundant, which had been previously established by PALMBERG for Finnish material. Yet BSP tests differing from the normal were about equally numerous in association with high and low protein values.

If the foregoing criteria are applied, it will be seen that the patients of this series could have normal BSP tests while evident anhydremia prevailed, while on the other hand high BSP retentions appeared without any sign of it. It may be maintained therefore that there is no direct correlation between hemoconcentration and BSP tests differing from the normal, even if they occur simultaneously in several patients.

Plasma minerals

In this connection, I do not consider it necessary to discuss in detail those changes in the plasma minerals (»fixed base») which are most frequently to be found in severe gastroenteritis (HAMILTON & al., HOAGH & MARPLES, KERPEL—FRONIUS, GAMBLE ,FANCONI & ROSSI, DARROW etc.). In explanation of these changes the concept of two phases of the diarrheal illness has been evolved (RAPOPORT & al.): 1) the phase of dehydration and acidosis, during which losses of extracellular and intracellular ions and fluids occur, and 2) the postacidotic phase, during which, after correction of deficits of extracellular ions, depletion of the nonextracellular ions ensues because of avid uptake of these ions by soft tissues and bone. With completion of the process of cellular restitution normal equilibrium between intracellular and extracellular phases is reestablished with return to normal of the levels in plasma. Therefore the concentration of certain electrolytes represents in this phase the resultant between supply and demand, and we do not know all the factors involved.

Considerable dissimilarity could be observed in this respect in the patients of this series, evidently due e.g. to the duration of disease before admission and the treatment then used. It is generally recognised that dehydration and anhydremia can produce hypersalemic values, although an evident demineralisation of the organism is in progress (KERPEL—FRONIUS, FANCONI etc.). I shall confine myself to describing some typical cases. On admission, both plasma sodium and plasma potassium values were low in cases 27, 28, 38, 41 and 42, and they surpassed the normal in cases 3 and 48. In addition, the sodium concentration was below the normal in cases 14, 22, 26 and 49, and the potassium concentration in cases 29 and 39. Plasma sodium surpassed the normal level, while potassium was simultaneously low, in cases 32, 40 and 45. A level of plasma potassium exceeding the normal was found in cases 2, 50 and 33, this latter having simultaneous low sodium values. The findings varied also in the postacidotic state.

72 simultaneous determinations of plasma sodium and potassium with a flame photometer (HALLMAN & LEPPÄNEN) and of the BSP test were performed with the following results:

Table 19. Plasma Sodium (mEq/l.)

BSP retention (mg %)	> 145	145—136	< 135
0 — 0.4	6	8	—
0.5 — 1.0	9	13	4
1.1 — 2.0	9	14	4
> 2.0	2	2	1
Total	26	37	9

Table 20. Plasma Potassium (mEq/l.)

BSP retention (mg %)	> 5.5	5.5—4.0	< 3.9
0 — 0.4	2	7	5
0.5 — 1.0	3	13	10
1.1 — 2.0	1	10	15
> 2.0	1	1	4
Total	7	31	34

About three fourths of the patients were treated with sodium and glucose solutions without parenteral potassium. This is also demonstrated by the results of these determinations, since plasma potassium was below 3.9 mEq/l. in about half of them. Plasma sodium exceeded 145 mEq/l. 26 times and remained below 135 mEq/l. 9 times. Low plasma potassium levels were found relatively more often in fatal cases, and these same patients also most frequently had BSP tests departing from the normal. The slightest and most transient changes in the plasma minerals were revealed by patients who were parenterally given DARROW's solution.

The results of simultaneous determinations show however, that all degrees of BSP retention appeared both while plasma potassium and sodium values were normal, and while they were above or below the normal level.

HOWLAND and MARRIOT, KRAMER, TISDALL and later RAPOPORT and coworkers have focused attention on hypocalcemia which is sometimes seen in diarrhea patients during the postacidotic phase, and which produces certain symptoms. This may be partly due to

bicarbonate medication, and calcium therapy seems to exercise a beneficial effect.

In my own series similar observations could be made in 14 patients, but 28 simultaneous determinations show that no correlation exists between the degree of BSP retention and the calcium concentration of the blood.

To summarise, it can be said that variations in mineral contents of the plasma and the results of BSP tests are not associated with each other.

Acidosis

HOWLAND and MARRIOT, SCHLOSS and STETSON, and YLPPÖ found during the first world war that plasma bicarbonate and pH were decreased in severe infantile gastroenteritis. The general opinion is that the promoting factors in the appearance of acidosis are the loss of minerals from the organism and circulatory disturbances typical of this disease, with ensuing anoxia, increased formation of organic acids and disturbed renal function.

Apart from the serious clinical picture presented by my patients they were also exceedingly grave cases where acidosis was concerned. In their recently published statistics, FLETT, PRATT and DARROW establish a dubious prognosis in cases with an alkali reserve below 15 mEq/l. at the beginning of treatment. Of my 50 patients 35 fell into this category, and 17 of them had on admission an alkali reserve of only 4—9 mEq/l. Twelve of the latter recovered however.

Simultaneous determinations of the plasma bicarbonate (LEHMANN) and of the BSP retention were performed 106 times, with the following results:

Table 21. Plasma Bicarbonate (mEq/l.)

BSP retention (mg %)	> 31	31—19	18—4
0 — 0.4	6	8	5
0.5 — 1.0	4	23	15
1.1 — 2.0	5	18	10
> 2.0	2	6	4
Total	17	55	34

Owing to the nature of the disease, a great number of determinations were performed on acidotic patients. The foregoing table illustrates, however, that all degrees of BSP retention were revealed by alkalotic patients as well.

Changes in the chloride concentration of the plasma are associated with the loss of minerals and acidosis. Hypochloremia is a common finding in gastroenteritis patients, even if hyperchloremia produced by dehydration and great deficiency of sodium can be found (HOAGH & MARPLES, CSAPÓ & al., FANCONI, PRADER & ROSSI). In addition, it has been demonstrated that chloride ions, as well as sodium, pass into red blood cells during dehydration and promote the diminution of the plasma chloride (VAN SLYKE, LEVY, KERPEL—FRONIUS, DARROW).

In my own series, 12 patients were unmistakably hyperchloremic on admission, 18 were hypochloremic, the chloride concentration being normal in the remainder. During treatment variations in either direction were seen. The patients were subjected to 120 simultaneous determinations of the plasma chloride (NaCl, SENDROY and the BSP retention, with the following results:

Table 22. Plasma Chlorides (mEq/l.)

BSP retention (mg %)	>106	106—97	<96
0 — 0.4	2	22	9
0.5 — 1.0	6	27	10
1.1 — 2.0	2	17	13
>2.0	1	6	5
Total	11	72	37

Even if a great part of the BSP tests was performed on hypochloremic patients, it is nevertheless evident from the table that there is no correlation between the plasma chloride levels and the BSP retention.

Azotemia

One of the characteristic features in severe infantile gastroenteritis is functional renal insufficiency, marked by diminished diuresis, albuminuria, cylindruria and a rise of the non-protein nitrogen in

the blood. Theories have been advanced in explanation of the appearance of this insufficiency (NOBECOURT & MAILLET, SCHLOSS, KERPEL-FRONIUS etc.). These symptoms were seen in several patients of my series, and 22 of them had increased non-protein nitrogen values on admission, which returned to normal while rehydration was in progress.

The results show that all degrees of BSP retention appeared simultaneously with both normal and increased non-protein nitrogen, and that no correlation between them could be established.

Discussion

The proper incentive to the present investigation was provided by fatty changes of the liver which are generally revealed by autopsies performed at our hospital on gastroenteritis patients. On the basis of these changes and of clinical observations, the literature has stressed again and again the role played by the liver in this disease and has assigned to its presumed functional disorder a more or less central position in various stages of this complex (CZERNY, FINKELSTEIN, SCHIFF, PFAUNDLER, BRÜNING, ROSENBAUM, FANCONI, MARIE & al., SCHLESINGER & al., GRÜNHOLZ etc.). THIEMICH had already argued the question in his time whether fatty metamorphosis should be interpreted as degenerative and due to a lesion of hepatic cells, but in spite of every effort an exhaustive answer still remains to be found.

So-called liver function tests have been infrequently performed on these patients, and only exceptional cases have given conclusive results (MARIE & al., SCHLESINGER & al., HALLMAN & KAUHTIO etc.). Since, moreover, the BSP test generally regarded as fairly reliable had not been applied in these papers, the present investigation seemed justified.

The BSP tests in my gastroenteritis series differ from those performed on normal material in similar age groups. The elimination of the dye from the blood stream was unmistakably slower than in healthy infants. Particularly the second phase of the elimination, interpreted as demonstrating the function of hepatic cells, was prolonged. Tests repeated in the course of one day gave similar indications. A disappearance of the dyestuff slower than normal was also revealed by the values of the BSP clearance coefficient calculated for gastroenteritis patients. These figures were low throughout, and their average was only half of that found in healthy infants.

The interpretation of results in BSP tests is based on the generally recognised opinion that the plasma volume is on an average 5 per cent of the body weight (GAMBLE), i.e. about 45—50 ccm/kg, even if it is known that individual variations can be considerable and due to several factors. Although this assumption harbours appreciable possibilities of error, thousands of BSP tests performed on adults have demonstrated that it does not have any practical significance, at least where variations occurring in normal individuals are involved. On this basis, and using a dosage of 5 mg dye per kilogramme of body weight, the theoretical BSP concentration in the blood would be 10 mg% at the time of injection.

It has been shown that the plasma volume in healthy infants approaches the above-named values, when using different dye methods for the determinations. Older investigations report higher values (LUCAS & DEARING: 42—78 ccm/kg, mean 67 ccm/kg; BAKWIN & RIWKIN: 38—72 ccm/kg, mean 61 ccm/kg), which is probably due to some extent to imperfect technique, as e.g. ROBINOW and HAMILTON have suggested. In later studies the figures are consistent (DARROW & al., SECKEL, BRINES & al.), and DE MARSH and coworkers assess the plasma volume at 46—47 ccm/kg in the newborn; according to RUSSEL, it is 46.1 ccm/kg at the age of 3—12 months determined with Congo red and Evans blue. GUEST and collaborators have obtained with isotopes plasma values of 36.4 ± 4.69 ccm/kg. It seems evident that healthy infants are fully comparable to adults in this respect.

The situation is different, however, when infants affected with severe gastroenteritis are subjected to the tests, an essential factor of their disease being changes in blood chemistry and circulation. In dehydration the blood is known to concentrate (HAMILTON & al., BEYER, SECKEL, GAMBLE) and its viscosity to increase (CZERNY, LUST, SURANYI & SONNAUER). The quantity of circulating blood is diminished (DARROW & BUCKMAN, SECKEL, DIECKHOFF), its velocity decreased (MARRIOT, UTHEIM) and the blood pressure reduced (TRUMPP, KHOKHOL, MARRIOT, SCHIFF). So-called circulatory collapse occurs, i.e. a disparity between the volume of blood vessels and the amount of circulating blood, which is of evident importance at this stage of the disease (KERPEL—FRONIUS). Proper treatment

can frequently relieve this condition, but it is largely a matter of conjecture for how long its effects persist.

Several of my patiens were on admission in the state of circulatory collapse, treated as a rule intravenously with plasma and blood, which were generally administered repeatedly. The first BSP test was performed after these therapeutic measures, in 12 to 24 hours, sometimes even later, while rehydration was already fully in progress. Yet it is evident that the effect of the general circulatory factors already described must be taken into account in assessing the appearance of a BSP retention differing from the normal.

Circulatory collapse is, however, associated with a factor, which evidently has a reducing influence on the BSP retention. BRAUER and PESSOTTI have shown that the dye is combined with the plasma albumin fraction, and in addition, it is known that because of the altered capillary permeability at the peak of the disease, albumin is the substance passing into the interstitial fluid (DARROW & BUCKMAN, LINNEWEH, DIECKHOFF, SCHWARZ—TIENE & MENGHI). It is probable that the dye is also simultaneously conveyed outside of the blood vessels, and its concentration in the blood is reduced.

Even if the patients have survived the acute stage of the disease, and rehydration has occurred, they cannot yet be placed on a level with healthy infants as far as the fluid balance is concerned (STOLTE, SCHIFF, MARRIOT, SCHAUER, STENGER etc.). Instead they are frequently, after prolonged semistarvation, wasted malnourished infants. It has been possible to demonstrate in several series that in this condition the volume of both plasma and extracellular fluid is as a rule above the normal, calculated per kilogram of body weight (MARRIOT, BAKWIN & RIWKIN, GOLLAN, HENSCHEL & al., MOLLISON, WALTERS & al., KERPEL—FRONIUS & KOVACH). This circumstance as such may have affected the BSP tests performed on my patients in the later phase of the disease, naturally in the direction of reducing the retention. A similar effect is evidently exercised by a prolonged infusion treatment (GILLIGAN & al.). On the other hand, fever is known to reduce the plasma volume (GIBSON & KOPP), so that daily variations can appear in either

direction. It seems, however, that these variations have the same extent as those appearing in comprehensive normal adult material, and therefore the results of BSP tests are hardly affected by them.

While the postacidotic malnutrition state prevails, there are on the other hand general circulatory factors whose significance should not be underestimated. MARRIOT and UTHEIM had already drawn attention to this, and using a calorimetric method, they found that the blood flow was decreased in the extremities. More recently KERPEL—FRONIUS and VARGA have studied the dynamics of circulation in infantile malnutrition, and found the cardiac output and blood pressure reduced, the circulation time longer than normal, and the capillary permeability increased. In their series there are no patients in the postdiarrheal state, but these observations can in all probability be applied as such to these patients.

When assessing the results of the BSP tests performed in my series in the light of the foregoing investigations, bearing in mind on the other hand those BSP retentions surpassing the normal which were found in the cardiac cases (BLUMBERG & SCHLOSS etc.), one is left with the impression that general circulatory factors and blood chemistry play an important part in my cases. The determinations of the blood volume and of circulation time simultaneously performed were of great assistance in the elucidation of this question, since it is probable that the excretory capacity of the liver, and other glands as well, is in relation to the amount of blood passing through them (RÄIHÄ). Taking into account the critical condition of the patients, as well as the numerous therapeutically necessary and exhausting procedures, there was no possibility to perform any extra tests. Determinations of the hepatic blood flow would yield particularly valuable data (BRADLEY & al. etc.), but the methods in use so far are unadaptable, if only for the reasons already stated.

The probable hemoconcentration and circulatory insufficiency may provide an explanation of the BSP retentions slightly departing from the normal, which were observed in the patients of my series during the first 2—3 days of treatment, even if it is far from always that the results of blood counts simultaneously show signs of anhydremia. Evaluation is complicated by the circumstances previously referred to. In the postacidotic state some patients also

appear to linger on the margin of circulatory failure, as KERPEL—FRONIUS and VARGA were able to demonstrate in infantile malnutrition.

In spite of the foregoing, it appears that general circulatory factors are not solely responsible for the BSP tests differing from the normal in my material. Cases were seen in fact whose retention did not differ from the normal, although this was to be expected on the basis of the blood examinations. On the other hand, quite considerable retentions appeared where no circulatory collapse could be established. Such observations could be made both by comparing different patients to each other, and by following the variations in the BSP retention of the same patient.

As already mentioned, observations concerning circulation, with the exception of typical circulatory collapse, are beyond the scope of the present investigation. On the other hand, the tables presenting the relation between the BSP retention and blood chemistry show that the appearance of positive BSP tests does not seem to have any clear correlation with the results of these investigations.

On admission several patients of this series were feverish, but the effect of temperature on the results of the BSP tests seems to be insignificant in this material, even if contradictory results have also been reported (HICKS & al.).

Starting from the assumption that enlarged liver was chiefly produced in my patients by fatty infiltration and that liver functions could be disordered by these circumstances, comparisons were made between the size of the liver and BSP retention. BSP tests differing from the normal were as a rule more frequent in those cases who suffered from gross enlargement of the liver, but could be seen also in patients with only a slightly enlarged or normal liver. On the other hand, some normal BSP tests were revealed by patients whose liver was evidently affected with strong fatty infiltration, even if the majority of normal tests were found while the liver size was normal. It seems evident that massive fatty metamorphosis of the liver predisposes to a BSP retention differing from the normal, but the high reserve power of the liver and its regeneratory capacity (HIMSWORTH etc.) are able to eliminate this trouble, at least in part. This is supported by my material, in so far as the BSP tests

of recovered patients returned to normal, before a shrinking of the liver could be established. In some cases a temporary enlargement of the liver occurred only after the BSP tests had already returned to normal.

Furthermore, local circulatory factors may be implicated in positive BSP tests found in association with gross enlargement of the liver. In fact, it seems possible that the hepatic cells, loaded with fat at autopsy, exercise, while expanding and flattening the nuclei, pressure on the capillaries, thereby reducing the hepatic blood flow. At autopsy, massive fatty liver is known to be quite bloodless as compared to a liver affected with slighter fatty changes, in which congestion is often seen in such patients (AHVENAINEN). Similar pressure can be assumed to be exercised also upon the bile capillaries, resulting in interference with the bile secretion and a delayed excretion of the BSP. The occurrence of jaundice found in some diarrhea materials (GAIRDNER, GILES & SANGSTER, SCHLESINGER & al.), which, however, was not manifested in my series, may be explained in this way. As already mentioned, AHVENAINEN was able to demonstrate in hepatic capillaries of these patients hemosiderin masses, which can be interpreted as thrombus formations and which evidently affect the hepatic blood flow. These investigations are, however, still in progress, and the opinions expressed above are only conjectures, but their role in the appearance of BSP tests differing from the normal cannot be entirely disregarded.

The tendency to hemorrhages and a prolonged prothrombin time in infants affected with diarrhea has been interpreted as being due to disturbed liver function. In our earlier investigations we came to the conclusion that this was largely due to reduced absorption of vitamin K from the intestine and its deficiency in the diet. While the liver is functioning well, the prolonged prothrombin time can be quickly reduced to normal by giving vitamin K parenterally, but in 8 cases in our series the reaction was not normal, which was interpreted as an indication of disordered hepatic function (HALLMAN & KAUHTIO).

In this series the reaction to vitamin K was not studied systematically, but it was found to differ from the normal in 22 patients. Twelve of them recovered, who all had a delayed reaction to vitamin K. Among the fatal cases, 2 had a delayed reaction and in 8 it was entirely absent. Functional disorder of the liver therefore

seems evident in these cases and appears moreover to prophesy a fatal outcome. In patients whose reaction to vitamin K differed from the normal, enlarged liver was generally found during the disease, even if it was not always simultaneous with the abnormal vitamin K test. All the patients just mentioned had BSP tests differing from the normal.

Variations in the BSP retention were almost regularly associated in individual patients with changes in the general condition. The disappearance of the toxic state during the first days of treatment was invariably reflected in a reduced BSP retention. Similarly, an increased BSP retention was often found if the general condition deteriorated, while the patient again became tired, listless, and looked more ill, even if the fluid balance, assessed by means of determinations from the plasma, remained satisfactory the whole time. It can be clearly seen in some cases how the increase in BSP retention precedes such a turn for the worse in the patient's condition. Similar observations could be made in fatal cases. If the duration of the disease was under two weeks, the BSP tests were generally positive the whole time, and the retention increased as death approached, which could be seen as well in some patients with a longer illness. In all those patients who recovered, the BSP tests returned to normal before their discharge, and almost regularly coincided with the beginning of clinical improvement. Four individual patients revealed a higher BSP clearance coefficient while clinical improvement was in progress (Cases 2, 22, 24 and 31). Similarly, in 2 fatal cases (Cases 49 and 50) a reduced coefficient was a mark of a decreased excretory capacity of the liver, which in its turn can be regarded as some kind of a measure of the general functional power of the organism.

On the basis of the foregoing bedside observations, it is evident that variations of the BSP retention in individual patients are in correlation with their general condition and the picture of the disease. This opinion is also supported by the pronounced difference in the average time of treatment of the recovered patients, since in the third group of my material, which had positive BSP tests for several weeks, the average duration of treatment was two weeks longer than in those patients who only had such tests during the two first weeks of treatment.

The opinion that the infant organism is injured in some way in the course of severe gastroenteritis can be met with, under different aspects, in practically every publication dealing with this complex. It is also evident that several factors produce this lesion, as has been demonstrated in various investigations.

Symptoms of such undefined injury can be seen in abundance after acute stage in these patients. Tolerance to food is often low and the gain in weight slow (FINKELSTEIN, DARROW, etc.), the capacity to bind the fluids is practically nonexistent (STOLTE, SCHIFF, STENGER), and the tendency to anemia, hypoproteinemia and edema is pronounced. Sometimes a typical state of postacidotic athrepsia (MARRIOT) can be seen, when the patients are wasted and apathetic, have a poor appetite and may vomit profusely, and the recovery progresses very slowly. This condition is also associated with a tendency to hemorrhage (RAPOPORT & DODD etc.), a high predisposition to infection, and clinical symptoms of nervous disorders (YLPPÖ).

Recent investigations have suggested that these phenomena are due, in addition to extracellular variations, to changes in the composition of individual cells, possibly more than to any other factor. Some older papers advance theories according to which body cells entirely disintegrate in the course of severe gastroenteritis (MEYER, JUNDELL etc.). In conformity to tissue analyses and balance tests (TOBLER, KERPEL—FRONIUS, DARROW), the determinations of potassium and sodium in erythrocytes during severe gastroenteritis, performed by HALLMAN, demonstrate that cell minerals undergo extensive changes, while the organism apparently attempts to counteract them as speedily as possible, with variable results. According to modern opinion, potassium balance is of particular significance, and e.g. in DARROW's latest material, treated with parenteral potassium, there are no postacidotic athrepsia states at all. One may venture to expect, that with a further development of the methods it will be possible to demonstrate, in addition to mineral changes, some other alterations occurring in individual cells and vitally affecting organic functions.

In our investigations dealing with the volume of extracellular fluid in severe gastroenteritis by the thiocyanate method (HALLMAN & KAUHTIO), we came to the conclusion that factors regulating

cellular permeability and selectivity with regard to electrolytes, are disturbed. Under normal conditions the thiocyanate ion is, practically speaking, extracellular, but in the course of the disease it was found that thiocyanate space generally exceeded the normal, even approaching in some cases the total amount of fluid in the body. This can hardly be explained in any other way than by the penetration of thiocyanate ions into the cells. It was found that this phenomenon was clearly correlated with the migration of minerals in red blood cells, and it was a reversible condition.

Twentynine cases in my series are of particular interest. These patients were subjected to determinations of potassium and sodium in erythrocytes, and simultaneously, to BSP tests. The majority of them reveal a fairly clear correlation between potassium deficiency in red blood cells and an increased BSP retention, and on the other hand, between the clearing-up of potassium deficiency and the lowering in BSP retention (HALLMAN & KAUHTIO).

When assessing, on the foregoing basis, the BSP tests of my material differing from the normal, it becomes evident that circulatory collapse, supervening when the disease has reached its peak, clearly promotes increased retention. The possible inferiority in circulation can have a similar effect even in the later stage. Gross fatty infiltration of the liver seems to contribute towards increased retention, due either to excretory insufficiency of the cells, or to a reduced hepatic blood flow.

Yet there are some BSP tests differing from the normal in my series, in connection with which the factors increasing retention and described above could not be observed. On the other hand, it has been demonstrated that some basic properties of the cells undergo changes in the course of the disease, and return to normal when recovery sets in. It must be therefore regarded as highly probable that the observed changes in cell minerals and disturbances in cellular permeability or selectivity are in some way related to the altered and deficient organic function of the cells, associated with the complex of severe gastroenteritis. The BSP tests differing from the normal found in the patients of my series can be considered as a manifestation of this disturbed function in liver cells, which is also suggested by the results of vitamin K tests performed in this study.

Conclusions

1. The elimination of bromsulphalein from the blood stream is slower in infants suffering from severe gastroenteritis than in healthy infants of the same age. This produces BSP tests differing from the normal, whose occurrence in the patients of my series seems to be in correlation with the patients' general condition and the course of the disease.

2. General and local circulatory factors probably play an important part in the appearance of BSP tests differing from the normal in gastroenteritis patients. No direct correlation to the blood chemistry, liver size or body temperature can be demonstrated.

3. BSP tests differing from the normal and a lower BSP clearance coefficient probably indicate in several patients of this series, that the excretory capacity of the liver cells with regard to BSP was poorer than normal during the disease. This can be interpreted as a mark of changes occurring in the liver cells during severe gastroenteritis. A similar indication is given by the vitamin K tests differing from the normal found in my material.

C. Summary

Present study attempts to elucidate the liver function in severe infantile gastroenteritis. For this purpose the author has performed bromsulphalein tests which had not been previously studied in these patients. Elimination of bromsulphalein from the blood stream was studied in healthy infants aged from 2 weeks to 12 months (30 cases), and in patients of this age affected with severe gastroenteritis (20 cases), using a dosage of 5 mg dye per kilogram of body weight. In both series this removal was found to occur in two phases, of which the first rapid one was apparently identical with that observed in adults. The second, usually interpreted as illustrating the function of liver cells, was found to be slower in this material than in adults, and moreover, it was slower in infants suffering from gastroenteritis than in healthy babies of the same age. Individual variations were considerable, but the capacity to eliminate the dye seems to increase with age. Likewise, the BSP clearance coefficient was found to be lower in this series than in healthy adults, and apparently it also rises with advancing age. The average value of the clearance coefficient in infants suffering from severe gastroenteritis (25 cases) was lower than in healthy infants (24 cases), but individual variations were considerable.

The normal values in usual BSP test, in which 5 mg of the dyestuff were given per kilogram of body weight and the retention in the serum was determined in 45 minutes, was assessed by the method used at 0—0.4 mg% in healthy infants aged from 2 weeks to 12 months (56 cases). The results of the BSP tests did not seem to be affected by the time of day.

Of 50 patients suffering from severe gastroenteritis 46 had BSP tests differing from the normal, generally several times in the course of the disease. With the object of throwing light on this phenomenon, the possible correlation of the BSP retention to blood chemistry was studied by comparing the results to the

levels of hemoglobin, erythrocytes, hematocrit, plasma proteins, sodium, potassium, calcium, bicarbonate, chlorides and non-protein nitrogen, simultaneously determined in these patients. No clear correlation could be seen. Nor was any correlation to body temperature observed.

The degree of the BSP retention was also compared to the liver size of the patients, starting from the assumption that an enlargement of the liver was due to fat infiltration. It was noted that with the appearance of gross fatty changes, the BSP tests regularly differed from the normal. In addition, the retention was also compared to simultaneous determinations of the prothrombin time and the results of vitamin K tests. The former did not reveal any correlation. In eight fatal cases the reaction to vitamin K was entirely absent, in addition, it was slower than normal in 14 cases, 2 of whom died. All these patients had BSP tests departing from the normal.

A study of BSP tests in individual patients indicated that an altered retention was frequently associated with changes in the patient's general condition, and an increased retention often prognosticated a turn for the worse, enlarged liver or a fatal outcome. Likewise, the retention returned to normal not later than at the beginning of clinical improvement, although the liver could be still strongly enlarged at the time. In six cases studied variations of the BSP clearance coefficient were fully in accordance.

In the discussion the writer reviews those factors which may affect the occurrence of BSP tests differing from the normal in this series, and attributes the greatest significance to general and local circulatory disturbances, which were evident in these patients even after the acute stage of the disease, but which are difficult to assess. Yet it appears probable that demonstrable alterations in body cells occurring in the course of the disease are responsible at least to some extent. Therefore the author advances the opinion that BSP tests differing from the normal and lower clearance coefficients in several gastroenteritis patients of this series can be interpreted as a manifestation of disturbed liver function, also indicated by vitamin K tests differing from the normal.

D. CASE REPORTS

Recoveries

Group I

Case 1. *No.* 747/49. *Pneumonia l. dx. Gastroenteritis.*

The birth weight was 3.800 g. The patient fell ill with cough and fever on Febr. 6, 1949, and two days later his stools became loose and streaked with blood. On admission Febr. 10, the general condition was fairly good. The weight was 4.100 g, T. 38^0. He was slightly dehydrated. Rales were pronounced in both lungs. He vomited and the stools were slimy, loose and green. Thorax rtg: Pneumonia l. dx.

4 / 3. he was still feverish. The weight was 3.500 g. Diarrhea was aggravated and the vomiting continued. Alk. R 52 vol %. BSP retention 0.3 mg %.

16 / 3. The fever abated. The patient was alert, diarrhea had stopped. Lungs, nil. BSP retention 0.2 mg %.

On March 31 he was discharged in good health. The weight was 4.200 g.

Comment: a boy aged 2 months who was admitted suffering from cough, fever and mild diarrhea. During the treatment pneumonia was found, and the patient was feverish, vomited slightly and had loose stools for 4 weeks. The BSP tests remained normal during his residence in hospital.

Case 2. *No.* 3156/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 4.850 g. The onset of diarrhea occurred on Sept. 6, 1949, when the patient was put on commercial milk instead of milk powder. He vomited profusely for 3 days and his condition was poor.

On admission Sept. 19, he was dehydrated, of a greyish pallor, and reacted feebly. Lungs, nil. Liver impalpable. Diarrhea ++. Hb. 74 %, R.B.C. 3.22 mill., hematocrit 31. Plasma proteins 6.2 g %, chlorides 600 mg %, Alk. R 35 vol %, non-prot. N 33 mg %. He was somewhat more lively on the following day. Alk. R 40 vol %. BSP retention 0.4 mg %.

25 / 9 diarrhea still continued. The patient was edematous. BSP retention 0.2 mg %.

3 / 10. He was alert and ate well. The weight increased. BSP retention 0.2 mg %.

Comment: a boy of 5 months was admitted to hospital in a poor condition. He was treated with parenteral potassium and made a good recovery.

During the disease plasma potassium remained normal, calcium was delayed, and the patient was discharged in 4 weeks. The BSP tests were normal.

Case 3. *No.* 3212/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.500 g. The patient fell ill on Sept. 20, 1949, at the orphanage, vomited, had diarrhea, and his condition became poor within two days. On admission Sept. 22, he was greyish, dehydrated and hollow-eyed. Reacted slowly to pinching. Lungs, nil. The liver was not palpable. Hb. 89 %, R.B.C. 3.81 mill., hematocrit 36. Plasma proteins 7.1 g %, chlorides 545 mg %, Alk. R. 29 vol %, non-prot. N 35 mg %. Diarrhea ++. The next day he felt unmistakably more active. Alk. R 47 vol %. BSP retention 0.4 mg %.

27/9. Vomiting and diarrhea continued. The patient was slightly edematous. BSP retention 0.2 mg %.

8/10. He was alert and ate well. Slight cough and rhinitis were present, but the diarrhea had stopped. BSP retention 0.4 mg %.

23/10. There was no gain in weight, although he ate fairly well. The cough persisted. BSP retention 0.2 mg %.

16/11. The patient was discharged.

Comment: a boy of 2 months and 2 weeks who fell ill at the orphanage and was admitted in a poor general condition and severely acidotic. He was treated with parenteral potassium, but he had an intercurrent respiratory infection and was discharged in 9 weeks. The BSP tests remained normal.

Case 4. *No.* 3271/49. *Gastroenteritis. Intoxicatio. Pneumonia l. dx.*

The patient had been under treatment in hospital because of pyloric stenosis. Immediately on his return home he fell ill with diarrhea and was readmitted one week later. On admission Sept. 26, 1949, he was tired, distressed, of a greyish colour and dehydrated. Lungs, nil. Diarrhea ++. Hb. 90 %, R.B.C. 4.26 mill, hematocrit 32. Plasma proteins 5.3 g %, chlorides 600 mg %, Alk. R 30 vol %, non-prot. N 37 mg %. Two days later he was better. He had slight fever and severe diarrhea. Alk. R 52 vol %. BSP retention 0.3 mg %.

5/10. He had fever and cough but no diarrhea. Thorax rtg: Pneumonia l. dx. BSP retention 0.3 mg %.

17/10. He was afebrile. The weight showed a pronounced tendency to increase. Lungs, nil. The patient was discharged as convalescent.

Comment: a boy aged 3 months who had been treated for pyloric stenosis was readmitted suffering from severe diarrhea. He was treated with parenteral potassium and was discharged in 3 weeks having recovered from slight pneumonia. The BSP tests were normal.

Group II

Case 5. *No.* 626/49. *Praematura. Gastroenteritis. Stenosis pylori hypertrophica.*

The birth weight was 2.200 g. At the age of 1 month the baby began to cough and was feverish. Tree days later vomiting occurred and the stools became loose. On admission Jan. 31, 1949, she was pale, thin and dehydrated. Weight 2.900 g. No acidosis. Thorax rtg: 0.

She seemed to make a good recovery, until on Febr. 21 excessive vomiting set in. Diarrhea ++. She lost 400 g. Alk. R 56 vol %. BSP retention 0.7 mg %.

28 / 2. She was tired, of a greyish pallor and hollow-eyed. Reacted slowly. The vomiting was profuse and streaked with blood. Plasma proteins 5.4 g %, chlorides 460 mg %, Alk.R 91 vol %. BSP retention 0.8 mg %.

2 / 3. The fever had abated, but the patient was still listless. The weight was 2.300 g. The pylorus was palpable. BSP retention 0.2 mg %.

21 / 3. Pyloromyotomy was performed. She made a good recovery and was discharged on April 4, 1949.

Comment: The patient was a premature baby of 1 month affected with respiratory infection and mild diarrhea. During her residence in hospital she had a renewed attack of diarrhea and was at times in a very poor condition. She was found to be pylorostenotic, was treated surgically and made a good recovery. During severe diarrhea her BSP tests were different from the normal.

Case 6. *No.* 855/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.020 g. Onset of fever, vomiting and diarrhea occurred on Febr. 15, 1949. The general condition deteriorated rapidly and on admission 19/2. the patient was strongly dehydrated and listless, greyish and halfconscious. T. 39^0, lungs, nil. The abdomen was distended and the liver palpable for 1 fb. Respiration, Cheyne-Stokes. The vomiting was profuse and the stools were slimy, watery and mixed with blood. Hb. 93 %, R.B.C. 4.16 mill., hematocrit 40, plasma proteins 5.9 g %, chlorides 515 mg %, non-prot. N 30 mg %, Alk.R 26 vol %.

Three days later the patient was still acidotic, Alk.R 30 vol %, but the general condition had improved. The liver was palpable for 2 fb. Diarrhea and vomiting ++, BSP retention 1.1 mg %.

25 / 2. he was still tired and feverish. Lungs, nil. Acidosis cleared up slight edemas. The stools were mixed with blood. Three days later the general condition improved in the nature of a crisis. The vomiting stopped, the stools were better. BSP retention 0.2 mg %.

15 / 3. Recovery was uneventful. The liver was palpable for 1 fb. He was discharged. BSP retention 0.2 mg %.

Comment: a boy of 6 months with no history of previous illness, contracted diarrhea, was acidotic for 3 days and feverish for more than a

week. The BSP test was different from the normal only during the first week of illness. Reaction to vitamin K was slower than normal.

Case 7. No. 861/49. *Gastroenteritis. Intoxicatio.*

Birth weight 3.520 g. Fell ill on Febr. 16, 1949, with fever, vomiting and diarrhea with a rapidly deteriorating general condition. On admission Febr. 20, the patient was dehydrated, halfconscious, of a grey tint and hollow-eyed. Lungs, nil. Cough and rhinitis were present. Hb. 111 %, R.B.C. 4.52 mill., Hematocrit 48. Plasma proteins 6.3. g %, chlorides 475 mg %, Alk.R 32 vol. %, Non-prot. N 75 mg %. Diarrhea ++. Acidosis was cleared up in two days, but the patient's general condition was still poor and he was slightly edematous. BSP retention 3,5 mg %.

26/2. he was evidently better but the fever persisted. Thorax rtg:0. The abdomen was tense, the liver palpable for 1 fb. He had convulsions at times. Diarrhea was better. Alk.R 70 vol %, BSP retention 0.9 mg %.

4/3. the patient felt more active, the fever had abated. The stools were mixed with blood, the liver was palpable for 2 fb. BSP retention 0.5 mg %.

11/3. he ate well, but there was as yet no gain in weight. Liver, nil.

17/3. he was discharged in a good condition. BSP retention 0.4 mg %.

Comment. a boy of 3 months with previously good health, who was affected with diarrhea, cough and rhinitis while the whole family was down with »influenza». He made a good recovery and was discharged after an illness of 4 weeks' duration. During the first two weeks of treatment the BSP tests differed from the normal and the reaction to vitamin K was delayed.

Case 8. No. 905/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.750 g. The patient was affected with severe diarrhea and profuse vomiting. The condition became poor in three days and there was an alarming loss of weight surpassing 1 kg. On admission Febr. 23 he was severly dehydrated, fully unconscious and of a greyish pallor. Lungs, nil. The liver was palpable for 2 fb. Hb. 114 %, R.B.C. 6.78 mill., Hcr. 50, plasma proteins 7.4 g %, chlorides 600 mg %., Alk.R 23 vol %, Non-prot.N 68 mg %. The vomit was streaked with blood, and the stools were watery, copious and offensive. BSP retention 0.6 mg %. Three days later the patient was still acidotic, but he had felt better in the meantime. BSP retention 0.2 mg %.

4/3. he did not vomit anymore and the diarrhea had stopped. The liver was palpable for 1 fb., BSP retention 0.1 mg %.

11/3. Thorax rtg:0. The patient was pale and his appetite poor.

19/3. He was alert, the gain in weight was satisfactory. BSP retention 0.1 mg %.

Comment: a boy of 8 months with previously good health; on admission he was in a very poor condition and acidotic for three days. Yet he made a good recovery and was discharged after 4 weeks in hospital. A

BSP test differing from the normal was only seen at the beginning of treatment, when the patient had a pronounced hemoconcentration. His reaction to vitamin K was normal.

Case 9. *No.* 934/49. *Gastroenteritis. Intoxicatio. Otitis media suppurativa l. dx.*

The patient was operated on for hypospadia. Immediately on being discharged he began vomit profusely and severe diarrhea developed. He was readmitted on the following day, Febr. 25, 1949, in a poor general condition, unconscious and dehydrated. Lungs, nil. The abdomen was distended, the liver palpable for 1 fb., T.38°. He vomited intensely, diarrhea ++. On the following day he was still slightly acidotic, and his stools were mixed with blood. BSP retention 1.9 mg %. Three days later his colour had improved, but he was still listless. Plasma proteins 6.3 g %, chlorides 580 mg %, Alk.R 56 vol %. BSP retention 0.9 mg %.

4 / 3. The stools were better, the vomiting had decreased. The patient coughed and was feverish. Thorax rtg:0. There was some discharge from the right ear. Alk.R 51 vol %. BSP retention 0.7 mg %.

16 / 3. The patient was afebrile and alert. BSP retention 0.3 mg %.

25 / 3. he was active, happy and ate well. BSP retention 0.2 mg %.

Comment: a boy of 6 months operated on for hypospadia who, immediately on discharge, fell ill with severe diarrhea and was readmitted in a poor condition. He made a rapid recovery and could leave hospital in 4 weeks. During the most severe stage of the disease the BSP tests were different from the normal and came back to normal with the beginning of clinical improvement. The reaction to vitamin K was normal.

Case 10. *No.* 951/49. *Gastroenteritis. Intoxicatio.*

Birth weight 4.000 g. The patient fell ill with cough, fever, vomiting and diarrhea, and was admitted a week later, on Febr. 26, 1949 in a poor general condition; he was dehydrated, greyish and reacted slowly. He vomited profusely, partly blood. Diarrhea ++. T. 38.1°. Lungs, nil. The abdomen was distended, the liver palpable for 1 fb. Hb. 93 %, R.B.C. 4.58 mill., Hcr. 40, plasma proteins 5,8 g %, chlorides 540 mg %, Alk.R 36 vol %, Non-prot.N 70 mg %. The toxic condition cleared up in two days. He continued to vomit, the stools were streaked with blood. T. 39°. BSP retention 1.4 mg %.

4 / 3. He was better, but the stools were still loose. BSP retention 0.5 mg %.

11 / 3. diarrhea stopped, he began to eat well. BSP retention 0.2 mg %.

Comment: a normally-developed boy of 3 months, was severely intoxicated on admission, but improved rapidly and was discharged in 3 weeks. BSP tests returned to normal with the beginning of the clinical improvement.

Case 11. *No.* 1056/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 2.950 g. At the age of one month there was an onset of severe diarrhea. On March 1, 1949 the patient began to vomit again and the stools became loose. She was afebrile. On admission one week later she was almost unconscious, dehydrated and thin. She was cyanotic and vomited blood. Lungs, nil. The liver was palpable for 2 fb. Hb. 93 %, R.B.C 4.10 mill., Hcr. 42. Plasma proteins 5.8 g %, chlorides 500 mg %, Alk.R 19 vol %, Non-prot.N 49 mg %. Diarrhea ++. The next day she was still bad and practically unconscious. Alk.R 32 vol %. BSP retention 0.9 mg %.

1 5 / 3. Acidosis was cleared up, the patient felt more active and had begun to eat. BSP retention 0.1 mg %.

2 5 / 3. She had made a good recovery. BSP retention 0.1 mg %. The patient was transferred for treatment to the orphanage.

Comment: a girl aged 3 months who had a relapse of diarrhea and was admitted in a very poor condition and severely acidotic. She recovered nevertheless and was discharged after 4 weeks. The BSP test differed from the normal only at the beginning of treatment. The reaction to vitamin K was normal.

Case 12. *No.* 1317/49. *Praematurus. Gastroenteritis. Stenosis pylori hypertrophica.*

The baby was born 4 weeks before the expected date of confinement. The birth weight was 2.300 g. At the age of 1 month he began to vomit, his stools became loose and offensive. On admission April 2, 1949 the general condition was poor, the patient was thin and dehydrated. Temperature subnormal. Lungs, nil. The liver was palpable for 1 fb. Hb. 93 %, R.B.C. 4.59 mill. Hcr. 42. Plasma proteins 4.1 g %, chlorides 585 mg %, Alk.R 41 vol %, Non-prot.N 41 mg %. Three days later diarrhea was still in progress. The patient had a subnormal temperature and was listless. BSP retention 0.5 mg %.

1 2 / 4. The vomiting continued. Alk.R 67 vol %. Peristalsis could be seen in the abdominal wall. BSP retention 0.4 mg %.

1 9 / 4. The patient was vomiting less and felt better. BSP retention 0.4 mg %.

2 2 / 4. Pyloromyotomy was performed. She made a good post-operative recovery and was discharged one month later.

Comment: a premature baby aged 1 month and 2 weeks who contracted mild diarrhea. In the course of treatment a hypertrophic pylorus was found and operated on. The patient made a good recovery. The BSP test differed only once from the normal.

Case 13. *No.* 1384/49. *Gastroenteritis. Lues congenita medicata.*

The birth weight was 3.450 g. Ever since her birth the patient had been at the hospital for syphilitic children, under penicillin treatment. Wasser-

mann:—. An epidemic having broken out at the hospital, the patient came down with diarrhea and her weight fell abruptly by 700 g within a few days. On admission, April 7, 1949, she was tired and pale. Lungs, nil. Liver and spleen were not palpable. Diarrhea ++. Hb. 68 %, R.B.C. 3.36 mill., Hcr. 33, Plasma proteins 5,7 g %, chlorides 620 mg %, Alk.R 40 vol %, Non prot.N 20 mg %. Acidosis was cleared up within the first three days, the patient was still listless. BSP retention 1.0 mg %.

14 / 4. she was more active. diarrhea had stopped. Wassermann:—. BSP retention 0.5 mg %.

21 / 4. the patient ate well, the weight increased. BSP retention 0.3 mg %.

Comment: a syphilitic girl aged 3 months, who fell ill during a diarrhea epidemic at the institution and made a good recovery during her residence in hospital of 3 weeks' duration. The BSP test was different from the normal at the beginning of treatment and came down to normal when clinical improvement set in.

Case 14. *No.* 1834/49. *Gastroenteritis.*

The birth weight was 3.900 g. The patient fell ill on May 10, 1949, with fever, cough and rhinitis. She vomited, and her stools were loose and slimy. On admission, May 15, the weight was 8.500 g, the patient was pale and looked ill. She coughed; lungs, nil. The abdomen was distended, and there were abundant petechiae on her limbs. Alk.R 24 vol %. The following night her temperature was 38.5. Convulsions occurred several times. Plasma calcium 8,3 mg %. Hb. 72 %, R.B.C. 4.10 mill., Alk. R 47 vol %. BSP retention 0.8 mg %.

26 / 5. the weight was 7.500. There was no diarrhea. BSP retention 0.3 mg %.

5 / 6. the weight was 7.000 g. She was fairly alert and ate moderately well. BSP retention 0.2 mg %.

26 / 6. the weight was still 7.000 g, but the patient felt active and ate well. BSP retention 0.2 mg %.

11 / 7. the weight was 7.600 g. She was discharged as convalescent.

Comment: a girl of 9 months with previously good health, who fell ill with respiratory infection and diarrhea. On admission she was slightly acidotic. The weight continued to fall for 4 weeks and began to increase only in the 8th week. During the first week of treatment she had convulsions, the blood calcium was low and her skin showed petechiae. The BSP test differed from the normal only att the beginning of treatment, but the reaction to vitamin K was delayed two times.

Case 15. *No.* 2208/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 4.150 g. The onset of diarrhea occurred on June 10, 1949. On admission a week later the patient was unconscious, dehydrated

and of a greyish pallor. Lungs, nil. Diarrhea ++. Plasma proteins 6.3 g %, chlorides 400 mg %, Alk.R 16 vol %. BSP retention 1.2 mg %. Next day her general condition was improved, but she vomited profusely. Hb. 86 %, R.B.C 4.18 mill., Hcr. 42. Alk.R 27 vol %. BSP retention 0.5 mg %.

2 4 / 6. The stools were still loose. Alk.R 71 vol %. BSP retention 0.2 mg %.

1 5 / 7. The condition was good. BSP retention 0.2 mg %.

Comment: a girl aged 1 month and 2 weeks, who on admission was in a poor general condition and severely acidotic. She recovered fairly rapidly from her acute stage, but began to gain in weight only in the 4th week of treatment. The BSP test was different from the normal only at the beginning of treatment. The reaction to vitamin K was slow.

Case 16. *No.* 2230/49. *Gastroenteritis. Stenosis pylori hypertrophica.*

The birth weight was 3.250 g. At the age of 2 weeks the stools became loose, the baby began to vomit and to lose weight. On admission, June 20. 1949, the weight was 2.550. He looked tired and ill, was thin and dehydrated. Lungs, nil. The stools were loose, green and offensive. Hb. 153 %, R.B.C. 6.28 mill., Hcr. 54, Plasma proteins 5.3 g %, chlorides 555 mg %, Alk.R 55 vol %. BSP retention 0.8 mg %. Three days later the diarrhea stopped. The patient still vomited. BSP retention 0.6 mg %.

3 0 / 6. he continued to vomit. Peristalsis was seen in the abdominal wall. BSP retention 0.5 mg %.

1 1 / 7. the weight was 2.600 g. Rtg: Stenosis pylori.

2 9 / 7. Pyloromyotomy was performed; the patient made a good recovery and was discharged 2 weeks later.

Comment: a boy aged 1 month who at the age of 2 weeks began to vomit and was affected with diarrhea, from which he made a rapid recovery in hospital, where pylorostenosis was found. Surgical treatment gave good results. The BSP test differed from the normal only at the beginning of treatment. The reaction to vitamin K was delayed.

Case 17. *No.* 2258/49. *Praematurus. Gastroenteritis.*

The birth weight was 2.400 g. The patient fell ill with diarrhea and vomiting on June 19, 1949, and was admitted 2 weeks later. He was in a poor general condition and weighed 2.500 g. The patient was thin and dehydrated. Diarrhea ++. Next day he was better. Hb. 80 %, R.B.C. 3.85 mill., Hcr. 40. Plasma proteins 5.5 g %, chlorides 600 mg %, Alk.R 38 vol %, Non-prot.N 33 mg %. BSP retention 1.2 mg %.

2 5 / 6. There was no diarrhea. Alk.R 44 vol %. BSP retention 0.5 mg %.

5 / 7. The patient was alert, the weight was increasing. BSP retention 0.3 mg %.

2 / 8. The weight was 3.000 g. BSP retention 0.2 mg %. The patient was discharged.

Comment: a premature baby aged 1 month, who fell ill with diarrhea and was admitted 2 weeks later. He rapidly recovered from the acute stage, but because of a slow gain in weight he was discharged only after the lapse of 7 weeks. The BSP test was different from the normal only in the initial stage of the disease.

Case 18. *No.* 2286/49. *Gastroenteritis Intoxicatio.*

The birth weight was 2.900 g. The patient fell ill on June 21 with diarrhea and vomiting. On admission, 5 days later, the general condition was poor. The patient was dehydrated, of a greyish pallor and unconscious. Lungs, nil. The abdomen was distended, the liver not palpable. Alk.R 25 vol %. During plasma infusion the patient went into shock. On the following day she was considerably better. Hb. 87 %, R.B.C. 3.89 mill., Hcr. 39. Plasma proteins 4.7 g %, chlorides 510 mg %, Alk.R 42 vol %, Non-prot.N 49 mg %. BSP retention 1.1 mg %. There was another plasma shock.

29/6. she was more active. The diarrhea had stopped. BSP retention 0.6 mg %.

5/7. The weight began to increase. BSP retention 0.2 mg %.

17/7. The patient was alert and was discharged. BSP retention 0.2 mg %.

Comment: a girl aged 2 months, who was inconscious on admission but made a rapid recovery and was discharged in 3 weeks. The BSP test differed from the normal at the beginning of treatment.

Case 19. *No.* 2288/49. *Gastroenteritis. Intoxicatio. Eczema infantum.*

Birth weight was 2.900 g. At times the patient used to have eczema of the face and limbs. The stools had also been loose now and then for a month's time. The condition deteriorated rapidly within a few days. On admission, June 27, the infant was thin and dehydrated, almost unconscious. Lungs, nil. The abdomen was distended. Diarrhea ++. Hb. 91 %, R.B.C. 4.86 mill., Hcr. 43. Plasma proteins 4.4. g %, chlorides 555 mg %, Alk.R 38 vol %. BSP retention 1.2 mg %. Two days later the general condition was better, with a longer interval between the stools, and acidosis was cleared up. BSP retention 0.7 mg %.

5/7. There was no diarrhea. The liver was not palpable. BSP retention 0.2 mg %.

18/7. The patient was lively and ate well, but the face and the limbs showed a reddish scaly eczema. BSP retention 0.2 mg %.

18/8. The gain in weight was poor. Eczema was still present. BSP retention 0.2 mg %.

18/9. The patient was still thin and listless. Eczema had disappeared, and the patient was discharged. BSP retention 0.2 mg %.

Comment: a baby of 9 months affected with eczema, in whom the diarrhea was rapidly overcome, but the eczema was aggravated, and therefore

the patient had to remain in hospital for 12 weeks. The BSP test was different from the normal only at the beginning of treatment. The reaction to vitamin K was normal.

Case 20. *No.* 2412/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.200 g. The patient fell ill at the orphanage with cough and fever, and was admitted to the hospital a week later. On admission July 8, 1949, she was thin, dehydrated, grey and hollow-eyed. Reacted slowly to pinching. T. 38.5°. Diarrhea and vomiting ++. Lungs, nil. The abdomen was distended, the liver was not palpable. The vomit was mixed with blood. Hb. 81 %, R.B.C. 4.19 mill., Hcr. 36. Plasma proteins 6.9 g %, chlorides 620 mg %, Alk.R 26 vol %, Non-prot.N 100 mg %. BSP retention 0.6 mg %.

10 / 7. The general condition was improved but she was still feverish. Stools and vomit revealed blood. Alk.R 67 vol %. BSP retention 0.2 mg %.

19 / 7. There was no diarrhea. The liver was palpable for 2 fb. The patient was listless and her appetite poor. Alk.R 90 vol %. BSP retention 0.7 mg %.

29 / 7. she was still tired. The liver was palpable for 1 ½ fb. BSP retention 0.4 mg %.

19 / 8. The general condition was good, the weight was increasing. BSP retention 0.2 mg %.

19 / 9. The gain in weight was 200 g in one week, the general condition was good. The patient was transferred back to the orphanage. BSP retention 0.2 mg %.

Comment: a poorly developed girl of 6 months who fell ill with diarrhea at the orphanage. On admission she was feverish and acidotic but quickly recovered from the acute stage. The gain in weight was, however, slow, and the patient was discharged only after 11 weeks' residence in hospital. The BSP test was different from the normal only at the beginning of treatment. The reaction to vitamin K was slow.

Case 21. *No.* 2415/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 2.900 g. Nine days before admission the patient fell ill with diarrhea and profuse vomiting. On admission, July 8, 1949, she was dehydrated, pale and unconscious. The weight was 3.200 g. The stools were watery and green. Alk.R 22 vol %. Lungs, nil. The liver was not palpable.

9 / 7. The general condition was improved, but she vomited profusely. Hb. 82 %, R.B.C. 3.90 mill., Hcr. 36, plasma proteins 4.9 g %, chlorides 565 mg %, Alk.R 32 vol %, Non-prot. N 60 mg %. BSP retention 1.0 mg %.

11 / 7. Diarrhea and vomiting continued. Alk.R 55 vol %. BSP retention 0.6 mg %.

19 / 7. The weight was 3.300 g. The vomiting ceased, and the stools were better. BSP retention 0.3 mg %.

10 / 8. She ate well and weighed 4.000 g. BSP retention 0.3 mg %.

19 / 8. The patient was discharged in good health.

Comment: a girl of 2 months was admitted in a very poor condition. She recovered nevertheless and was discharged after 6 weeks. The BSP test differed from the normal only at the beginning of treatment.

Case 22. *No.* 3259/49. *Praematura. Gastroenteritis. Intoxicatio. Otitis media l. sin.*

The birth weight 1.900 g. The baby was born 6 weeks before term. The onset of diarrhea and vomiting occurred at the age of 2 months. The weight decreased with 350 g. On admission a week later she was thin, dehydrated, listless and unconscious. Lungs, nil; slight rhinitis was present. The liver was palpable for 1 fb. The stools were watery, green and offensive. The weight was 2.300 g. Plasma proteins 6.5 g %, chlorides 630 mg %, Alk.R 15 vol %. BSP retention 0.6 mg %.

29/9. Weight 2.500 g. T. 39.5°. Convulsions. Plasma calcium 7.8 mg %. Diarrhea and vomiting ++. Alk.R 38 vol %. BSP retention 0.7 mg %.

3/10. The patient was unmistakably more active, she had begun to eat, but the stools were still loose and slimy. She was feverish, there was discharge from her left ear. BSP retention 0.5 mg %.

24/10. The weight was 2.350. She was fairly alert. The discharge of pus from her ear continued. BSP retention 0.2 mg %.

14/11. weight 2.500 g. BSP retention 0.2 mg %.

28/11. weight 2.950 g. She was alert and ate well. BSP retention 0.2 mg %.

Comment: a premature infant of 2 months, who on admission was in a very poor condition and severely acidotic. Yet the acidosis rapidly cleared up, but general recovery was slow and the patient could be discharged only after 10 weeks. In the acute stage the BSP tests were different from the normal.

Case 23. *No.* 3272/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 2.850 g. Two days after the onset of vomiting and diarrhea the patient was admitted to hospital, Sept. 27, 1949, in a poor condition. He was dehydrated, pale and reacted slowly. Lungs, nil. Diarrhea ++. Hb. 90 %. R.B.C. 4.12 mill., Hcr 41. Plasma proteins 4.6. g, chlorides 600 mg %, Alk. R 13 vol %. BSP retention 0.9 mg %. Two days later the condition was markedly improved, but diarrhea continued. Alk.R 54 vol %. BSP retention 0.5 mg %.

11/10. There was no diarrhea. BSP retention 0.4 mg %.

25/10. The patient made a good recovery and was discharged. BSP retention 0.2 mg %.

Comment: a boy aged 1 month and 2 weeks; on admission he was in a poor condition and severely acidotic. Yet he made a good recovery and was discharged in 4 weeks. The BSP test was different from the normal only at the beginning of treatment.

Case 24. No. 3289/49. Gastroenteritis. Intoxicatio.

The birth weight was 2.800 g. The onset of diarrhea and vomiting occurred on Sept. 26, 1949, and the patient was admitted 2 days later; she was then dehydrated, grey and reacted slowly. Lungs, nil. The stools were watery and slimy, the vomit was mixed with blood. Hb. 69 %, R.B.C. 3.34 mill., plasma proteins 6.5 g %, chlorides 545 mg %, Alk.R 33 vol %. BSP retention 0.7 mg %. Three days later the patient was livelier but the diarrhea continued. Alk.R 53 vol %. BSP retention 0.2 mg %.

10/10. she was more listless and vomited. BSP retention 0.5 mg %.

17/10. the patient was alert and ate well. The weight was increasing. BSP retention 0.2 mg %.

28/10. the general condition was good, she was discharged. BSP retention 0.2 mg %.

Comment: a girl of 3 months, who on admission was in a poor condition and slightly acidotic. She made a good recovery and was discharged in 4 weeks. The BSP test came back to normal at the beginning of clinical improvement.

Case 25. No. 3629/49. Gastroenteritis. Intoxicatio.

The birth weight was 3.000 g. At the age of 1 week the patient fell ill with cough, rhinitis and diarrhea. On admission, Oct. 10, 1949, she was dehydrated, grey and unconscious. Weight 2.450 g. Lungs, nil; the abdomen was distended. The liver was palpable for 1 fb. The stools were watery, offensive and mixed with blood. Hb. 144 %, R.B.C. 5.37 mill., Hcr. 64. Plasma proteins 7.2 g %, chlorides 560 mg %. Alk.R 15 vol %, Non-prot.N 61 mg %. Two days later the patient was still tired and the stools were loose. The vomit was mixed with blood. Alk.R 44 vol %. BSP retention 0.7 mg %.

2/11. the weight was 2.700 g, the condition better and no diarrhea. BSP retention 0.5 mg %.

9/11. the stools were loose again and the appetite poor. The liver was palpable for 2 fb. BSP retention 0.7 mg %.

16/11. the weight was 2.900 g. The patient was alert and ate well. BSP retention 0.3 mg %.

Comment: a girl of 2 weeks; on admission she was severely acidotic' dehydrated and deeply unconscious. She made an exceedingly good recovery, and was discharged in 3 weeks. The BSP test came back to normal as soon as clinical improvement set in.

Group III

Case 26. No. 1190/49. Gastroenteritis. Intoxicatio.

The birth weight was 3.450. The patient had been previously healthy, but the weight increased slowly. She fell ill with vomiting and diarrhea on March 11, 1949. Three days later she developed a cough, and the general

condition deteriorated. On admission March 21, the patient was listless and dehydrated, almost unconscious and with subnormal temperature. Lungs, nil. The stools were abundant, watery and offensive, the vomit was mixed with blood. The liver edge was palpable below the costal margin. Four days later the patient was still very tired. Acidosis cleared up. She had fever and a cough. Thorax rtg:0. Diarrhea and vomiting ++. BSP retention 1.3 mg %.

26 / 3. the general condition was still poor. BSP retention 1.7 mg %.

28 / 3. she was brighter. Diarrhea had diminished. BSP retention 0.4 mg %.

2 / 4. the patient was tired and listless again. No diarrhea. BSP retention 1.0 mg %.

5 / 4. she was fairly alert and ate well. Edema on the back and limbs. The liver was palpable for 1 fb. BSP retention 0.5 mg %.

10 / 4. the patient was more tired, vomited and had a poor appetite. No diarrhea. Liver palpable for 1 fb. BSP retention 1.0 mg %.

17 / 4. the patient began to eat, slight vomiting. The liver was palpable for 3 fb. BSP retention 0.3 mg %.

24 / 4. she ate well but was still thin and in a poor condition. The liver was palpable for 2 fb. BSP retention 0.3 mg %.

1/5. the improvement continued. The liver was palpable for 1 fb. BSP retention 0.2 mg %.

6 / 5. the patient was alert and ate well. BSP retention 0.1 mg %.

Weight and blood chemistry during disease

Date	21/3	25/3	26/3	28/3	2/4	5/4	10/4	14/4	1/5
Weight (gms)	3.800	3.900	3.900	3.900	3.800	3.900	3.600	3.600	4.000
Hemoglobin (%)	86	58	—	—	83	98	—	87	81
R.B.C. (mill.)	4.10	2.70	—	—	3.91	4.10	—	4.10	3.90
Hematocrit (%)	41	21	—	—	35	47	—	38	35
Proteins (g %)	5.9	5.0	4.7	5.7	4.5	4.9	4.7	5.4	5.8
Chlorides (mg %) ...	480	470	605	520	650	640	620	670	580
Bicarbonate (vol %)	27	43	60	53	48	47	60	50	54
Non-prot.N (mg %)	25	29	—	—	—	29	—	—	—
Sodium (mEq./1.) ...	129	137	150	151	142	154	161	150	155
Potassium (mEq./1.)	5.3	2.8	2.0	3.8	4.8	4.8	6.3	5.3	—
Calcium (mg %)	—	7.5	8.0	10.2	9.6	—	11.9	—	9.4
B S P (mg %)	—	1.3	1.7	0.4	1.0	0.5	1.0	0.2	0.2

Comment: a girl aged 3 months who was admitted in a poor condition and was acidotic for 5 days' duration. During the first week of treatment she revealed strikingly low plasma potassium levels, and calcium was low as well. In the initial stages she reacted poorly to vitamin K. The liver continued to grow up to the fourth week of treatment after which it began to diminish. Simultaneously the BSP tests were repeatedly different from the normal; they seemed to vary in accordance with changes in the general condition and returned to normal when clinical improvement set in, and while the liver was still enlarged. She was discharged as convalescent after 7 weeks' residence in hospital.

Case 27. *No.* 1216/49. *Gastroenteritis. Intoxicatio. Rachitis.*

The birth weight was 4.200 g. At the age of 1 month the patient had been affected with diarrhea. He fell ill again on March 17, 1949, and was admitted one week later. He looked severely ill, was thin, dehydrated and cyanotic. Rachitis ++. His reaction to pinching was feeble. T. 38^0, lungs, nil. The liver was not palpable. He did not vomit but the stools were loose and slimy. Two days later the general condition improved but the patient was still listless. He was feverish and coughed. Thorax rtg: 0. Diarrhea ++. BSP retention 1.3 mg %.

28 / 3. the patient felt fairly alert, but was still feverish. Lungs, nil. Ears, nil. BSP retention 0.6 mg %.

31 / 3. he was more listless again, and did not eat. The stools were mixed with blood. The liver was palpable for 2 fb. BSP retention 1.2 mg %.

5 / 4. he was still tired. Temperature normal. Diarrhea continued. Liver palpable for 3 fb. BSP retention 3.4 mg %.

8 / 4. There was a marked improvement. BSP retention 0.6 mg %.

13 / 4. the appetite was poor. He vomited somewhat and the stools were still loose. The liver was palpable below the navel. BSP retention 1.0 mg %.

21 / 4. the patient had begun to eat. The liver was unchanged. BSP retention 0.5 mg %.

28 / 4. his condition was good and the weight increasing. Liver palpable for 2 fb. BSP retention 0.3 mg %.

5 / 5. he was alert and happy. Liver palpable for 1 fb. BSP retention 0.1 mg %.

Comment: a boy of 4 months who had been previously affected with diarrhea. He fell ill again and was admitted to hospital, having been treated at home for a week, in an exceedingly poor condition. Slight acidosis cleared up in 2 days, but the general condition was poor for about 4 weeks and simultaneuosly the liver was strongly enlarged. The reaction to vitamin K was delayed. During the first week of treatment the plasma potassium level was very low. The BSP tests were repeatedly different from the normal during 4 weeks. With the beginning of clinical improvement the BSP retention returned to normal and the liver gradually diminished. The patient was discharged as convalescent after 8 weeks' residence in hospital.

Weight and blood chemistry during disease

Date	23/3	25/3	28/3	31/3	5/4	8/4	13/4	21/4	5/5
Weight (gms)	5.000	5.200	5.200	5.300	5.200	5.000	4.800	5.200	5.800
Hemoglobin (%)	80	60	57	66	68	68	—	95	98
R.B.C. (mill.)	4.34	3.41	2.76	3.33	3.40	3.30	—	4.66	4.60
Hematocrit (%)	43	27	25	29	34	29	—	45	45
Proteins (g %)	6.4	5.4	4.4	5.4	5.4	6.0	5.4	5.8	7.2
Chlorides (mg %) ...	420	605	570	530	580	650	670	620	620
Bicarbonate (vol %)	34	44	72	73	64	63	63	72	45
Non-prot.N (mg %).	45	16	36	—	40	18	—	27	—
Sodium (mEq./l.) .	116	135	141	138	145	153	151	145	138
Potassium (mEq./l.)	4.1	3.8	3.1	4.2	4.5	5.4	6.2	5.4	5.4
Calcium (mg %)	—	9.9	—	10.0	—	10.2	—	—	—
B S P (mg %)	—	1.3	0.6	1.2	3.4	0.6	1.0	0.5	0.1

C a s e 28. *No.* 1395/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.650 g. The patient had fallen ill a week before at the orphanage, and was admitted on April 9, 1949; he was then unconscious, dehydrated and hollow-eyed. T. 37,5°. He coughed, but the lungs revealed no abnormalities. The liver was palpable below the costal margin. The stools were watery and green. Next day the general condition was still poor, but acidosis cleared up. Diarrhea and vomiting ++. BSP retention 1.2 mg %, and in the evening 3.5 mg %.

11/4. he was still tired, diarrhea and vomiting continued. BSP retention 1.3 mg %.

15/4. the patient was listless.and the appetite was poor. T. 39°, thorax rtg: 0. The stools were better, there was no vomiting. BSP retention 1.7 mg %.

20/4. Temperature normal. Appetite improved. BSP retention 0.9 mg %.

26/4. diarrhea had stopped. BSP retention 0.4 mg %.

6/5. diarrhea had returned and the weight decreased. Yet he ate well. BSP retention 0.2 mg %.

14/5. the liver was palpable for almost 2 fb. BSP retention 0.2 mg %.

21/5. the patient was alert and ate well. The weight increased. BSP retention 0.2 mg %.

C o m m e n t : a boy of 2 months, who was admitted in a poor general condition. Acidosis was rapidly overcome, but BSP tests were different from the normal in the course of 3 weeks. Simultaneously the plasma potassium was low. The liver became enlarged while the disease ran its course, and the reaction to vitamin K was slower than normal. General improvement progressed slowly, and the patient was discharged in 7 weeks.

Weight and blood chemistry during disease

Date	9/4	10/4	13/4	16/4	20/4	26/4	6/5	21/5	28/5
Weight (gms)	4.050	4.300	3.900	4.050	4.200	4.200	4.100	4.200	4.500
Hemoglobin (%) ...	111	—	85	79	—	75	77	65	—
R.B.C. (mill.)	5.52	—	3.60	2.98	—	3.82	3.12	3.27	—
Hematocrit (%)	50	—	43	33	—	37	33	33	—
Proteins (g %)	6.5	—	5.8	4.6	5.0	—	5.5	5.0	5.6
Chlorides (mg %) ...	580	—	590	590	645	—	560	—	640
Bicarbonate (vol %)	22	45	47	58	65	—	36	53	50
Non-prot.N (mg %)	41	—	18	29	—	—	27	—	30
Sodium (mEq./l.) ...	141	—	138	133	154	—	155	141	139
Potassium (mEq./l.)	2.8	—	3.3	3.7	3.9	—	5.3	6.8	5.6
B S P (mg %)	1.2	3.5	1.7	—	0.9	0.4	0.2	0.2	0.2

Case 29. *No.* 1641/49. *Gastroenteritis.*

The birth weight was 3.150 g. The patient fell ill at the orphanage with vomiting and diarrhea and was admitted 10 days later. The weight loss was 500 g. On admission, April 29,1949, she was pale and severely dehydrated, listless but fully conscious. Lungs, nil. Liver not palpable. Diarrhea ++. BSP retention 0.5 mg %.

5 / 5. diarrhea had stopped, the patient was brighter. BSP retention 0.2 mg %.

1 3 / 5. the appetite was good, she began to gain in weight. BSP retention 0.3 mg %.

2 0 / 5. the weight decreased, the patient was listless and vomited. Diarrhea ++. BSP retention 1.1 mg %.

2 4 / 5. she was still tired and seemed toxic. No diarrhea. BSP retention 1.5 mg %.

2 7 / 5. the general condition was better, but the patient vomited profusely. BSP retention 0.6 mg %.

3 / 6. She was fairly alert, but continued to vomit. BSP retention 0.3 mg %.

2 7 / 6. she was lively and ate well. BSP retention 0.1 mg %.

Comment. a girl aged 3 months who fell ill at the orphanage with mild diarrhea, but the loss in weight was considerable. On admission she seemed at first to pick up but relapsed in 4 weeks, after which the improvement was slow and the patient could be discharged after a treatment of 9 weeks, duration. In the initial stages of the disease the BSP test was approximately normal, but during the relapse it differed repeatedly from the normal. Reaction to vitamin K was slow 2 different times. At the beginning of treatment and

Weight and blood chemistry during disease

Date	29/4	5/5	13/5	20/5	24/5	27/5	10/6	27/6
Weight (gms)	3.700	3.750	3.850	3.500	3.500	3.700	3.400	3.900
Hemoglobin (%) ...	79	72	87	—	81	104	—	90
R.B.C. (mill.)	4.00	3.47	—	—	4.20	4.54	—	4.10
Hematocrit (%)	38	35	—	—	40	45	—	40
Proteins (g %)	5.3	5.2	5.8	5.4	4.7	4.7	6.2	5.2
Chlorides (mg %) ...	470	700	635	545	600	660	575	580
Bicarbonate (vol %)	40	76	56	45	67	56	76	58
Non-prot.N (mg %)	100	27	—	—	—	28	—	—
Sodium (mEq./l.) ...	141	150	142	141	138	147	148	—
Potassium (mEq./l.)	3.1	2.9	4.2	6.2	4.0	3.8	4.3	—
B S P (mg %)	0.5	0.2	0.3	1.1	1.5	0.6	0.2	0.1

during the relapse the plasma potassium was low. The liver remained normal the whole time.

C a s e 30. *No.* 1697/49. *Gastroenteritis.*

The birth weight was 4.000 g. The patient fell ill at the orphanage with fever, diarrhea and vomiting, and was admitted 10 days later, May 5, 1949, in a fair general condition, but dehydrated and unmistakably thinner. The patient coughed, but lungs: 0. The abdomen was distended, the liver edge was palpable below the costal margin. The stools were loose, green and slimy. Two days later the general condition had deteriorated, diarrhea continued. BSP retention 2.6 mg %.

7 / 5. the patient vomited profusely. The liver was palpable 1 fb. BSP retention 4.5 mg %.

Next day the general condition was better. Diarrhea + +. BSP retention 1.8 mg %.

1 1 / 5. the stools were firmer. BSP retention 0.9 mg %.

1 8 / 5. diarrhea at times. Liver palpable for 2 fb. BSP retention 0.8 mg %.

2 5 / 5. the patient still had a poor appetite. No diarrhea, no vomiting. BSP retention 0.6 mg %.

2 / 6. he was alert and the appetite was better, the liver was palpable for 1 fb. BSP retention 0.4 mg %.

1 5 / 6. he was alert, the weight increased. BSP retention 0.4 mg %.

C o m m e n t : a boy aged 3 months, who had been ill with diarrhea at the orphanage for 10 days. He quickly recovered from acidosis, and in the initial stages of the disease the plasma potassium was low. Simultaneously the BSP test repeatedly and strongly differed from the normal, and returned

Weight and blood chemistry during disease

Date	6/5	7/5	11/5	18/5	25/5	2/6	15/6
Weight (gms)	4.400	4.600	4.700	4.500	4.300	4.400	4.700
Hemoglobin (%)	80	—	70	—	—	72	—
R.B.C. (mill.)	3.41	—	3.53	—	—	3.50	—
Hematocrit (%)	—	—	40	—	—	41	—
Proteins (g %)	5.7	5.4	5.4	4.8	5.4	—	6.1
Chlorides (mg %)	405	500	580	590	580	—	600
Bicarbonate (vol %)...	35	43	60	56	65	—	56
Sodium (mEq./l.)	139	—	143	146	—	—	—
Potassium (mEq.l.) ...	2.0	—	3.3	5.3	—	—	—
B S P (mg %)	2.6	4.5	0.9	0.8	0.6	0.4	0.4

to it with the beginning of clinical improvement. The liver was somewhat enlarged during the disease. The reaction to vitamin K was normal. The patient was discharged after 6 weeks.

C a s è 31. *No.* 1909/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.400 g. There was a sudden onset of diarrhea and severe vomiting, and the patient was brought to hospital on the following day. On admission May 20, 1949, he was practically unconscious, dehydrated and of a greyish pallor. Lungs, nil. The abdomen was tense, the liver not palpable. Diarrhea ++, the vomit was mixed with blood. He continued to vomit blood on the following day. T. 39,5°. BSP retention 0.6 mg %.

2 5 / 5. the patient was still quite listless, but the vomiting had stopped. He had convulsions now and then. Plasma Ca 7.6 mg %. BSP retention 0,9 mg %.

2 9 / 5. No diarrhea. There was blood again in the vomit. BSP retention 0.8 mg %.

3 / 6. he was still tired. Liver palpable for 1 fb. BSP retention 0.5 mg %.

1 0 / 6. he was alert, had begun to eat better. BSP retention 0.3 mg %.

2 3 / 6. he was alert and happy, the weight increased. BSP retention 0.2 mg %.

C o m m e n t : a boy of 2 months who, after one day of diarrhea, became severely acidotic and his general condition deteriorated. He made a good recovery from the acute stage. During it he had some convulsions and simultaneously the blood calcium level was low. BSP tests differed from the normal for 3 weeks, and the reaction to vitamin K was strongly delayed during the second week of treatment. The patient was discharged in 5 weeks.

Weight and blood chemistry during disease

Date	21/5	25/5	29/5	3/6	10/6	23/6
Weight (gms)	4.450	4.550	4.700	4.600	4.700	4.800
Hemoglobin (%)	77	58	—	—	—	80
R.B.C. (mill.)	3.94	2.74	—	—	—	4.44
Hematocrit (%)	33	30	—	—	—	40
Proteins (g %)	5.9	4.6	4.2	4.8	4.9	—
Chlorides (mg %)	570	545	575	645	700	—
B carbonate (vol %)	13	78	72	59	52	—
Non-prot.N (mg %)	100	32	—	—	—	—
Sodium (mEq./1.)	134	145	148	142	141	—
Potassium (mEq./1.).....	5.2	4.5	3.5	3.3	6.8	—
Calcium (mg %)	8.2	7.4	8,7	8.7	9.3	—
B S P (mg %)	0.6	0.9	0.8	0.5	0.3	0.2

C a s e 32. *No.* 2622/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 2,650 g. The patient had had several attacks of diarrhea during six months. Had been e.g. at this hospital in April for 3 weeks, in the course of which the BSP tests had been normal throughout. Later on she had been under treatment for diarrhea at another hospital for one month, and was admitted by us on August 1, 1949, after a new onset of acute diarrhea. Her general condition was poor. The patient was thin, dehydrated, pale, and reacted slowly to pinching. Lungs, nil. Liver palpable for 1 fb. No diarrhea, but some vomiting. Two days later acidosis cleared up, and the patient was more lively but edematous.

9 / 8. listless, no appetite. No diarrhea. Liver palpable for 2 fb. BSP retention 1.5 mg %.

1 4 / 8. she was still very tired, but the vomiting ceased. BSP retention 1.2 mg %.

2 1 / 8. the patient was more lively, had begun to eat. The liver was palpable for 3 fb. BSP retention 0.8 mg %.

4 / 9. she ate well, the weight showed a rising tendency. The liver was palpable for 2 fb. BSP retention 0.2 mg %.

4 / 1 0. she was alert. The liver was not palpable. BSP retention 0.2 mg %.

2 6 / 1 0. The general condition was satisfactory. The patient was small and thin, but alert and strong. BSP retention 0.1 mg %.

C o m m e n t : a girl of 6 months, who had had several attacks of diarrhea. She had been recently at another hospital for one month, but relapsed and was transferred to this hospital in a poor condition and acidotic. For one week the plasma potassium was low and the patient remained in a poor condition. The liver continually grew in size and the BSP tests were repeatedly

Weight and blood chemistry during disease

Date	1/8	5/8	9/8	14/8	21/8	4/9	4/10	26/10
Weight (gms)	4.500	4.600	4.400	4.400	4.400	4.600	5.000	5.600
Hemoglobin (%)	68	—	—	126	—	—	113	97
R.B.C. (mill.)	3.72	—	—	6.66	—	—	5.41	4.34
Hematocrit (%)	34	—	—	64	—	—	58	45
Proteins (g %)	6.1	4.8	4.2	6.2	5.6	5.6	5.8	—
Chlorides (mg %) ...	700	590	700	590	565	620	600	—
Bicarbonate (vol %)	23	59	47	44	49	61	43	—
Non-prot.N (mg %)	102	—	—	31	—	—	34	—
Sodium (mEq./l.) ...	154	142	149	146	144	150	—	—
Potassium mEq./l.)	2.7	3.4	4.6	4.2	6.0	5.0	—	—
B S P (mg %)	—	—	1.5	1.2	0.8	0.2	0.2	0.2

different from the normal, however, they returned to normal with the beginning of clinical improvement. While the liver was enlarged the reaction to vitamin K was slow. In view of the plasma shortage one had to recur to abundant amounts of blood i.v. (a daily dose of 50—80 ccm for a time of 3 weeks), in consequence of which the erythrocyte values were high. In addition, the patient was given lipocaic for 2 weeks, and one was left with the impression that this therapeutic measure had its share in her recovery from an apparently hopeless condition. The patient was discharged after 13 weeks' residence in hospital.

C a s e 33. *No.* 3390/49. *Gastroenteritis. Intoxicatio.* (*Lues congenita? Therapia prophylactica*)

The birth weight was 3.650 g. The mother had a positive Wassermann reaction during pregnancy, and was under penicillin medication, as well as the child. The patient fell ill at the institution on Oct. 4, 1949, with vomiting and diarrhea and was admitted 2 days later. He was dehydrated, of a greyish pallor and deeply unconscious. Lungs, nil. The liver was palpable for 1 fb. The stools were green, slimy and offensive. Next day the general condition had improved somewhat. T. 39^0. BSP retention 0.6 mg %.

1 0 / 1 0. he was still listless and feverish. Wassermann :—. BSP retention 0.4 mg %.

1 7 / 1 0. Temperature normal. He was more lively and had begun to eat, but the stools were still loose. Liver: no change.

2 6 / 1 0. No diarrhea. Liver palpable for 2 fb. BSP retention 0.9 mg %.

2 / 1 1. The appetite was poor and the patiĉnt vomited at times. Wassermann:—. BSP retention 1.0 mg %.

1 6 / 1 1. No gain in weight. Liver palpable for 2 fb. BSP retention 1.0 mg %.

21/11. The patient had begun to eat, the weight was increasing. The liver was palpable for 1 fb. BSP retention 0.4 mg %.

2/12. He was alert and well. BSP retention 0.1 mg %.

Weight and blood chemistry during disease

Date	7/10	10/10	17/10	26/10	2/11	9/11	16/11	21/11	2/12
Weight (gms)	3.150	3.050	3.150	3.300	3.350	3.250	3.300	3.400	4.100
Hemoglobin (%)	141	136	135	—	—	105	—	—	90
R.B.C. (mill.)	5.36	5.13	5.80	—	—	5.10	—	—	4.50
Hematocrit (%)	66	60	—	—	—	51	—	—	46
Proteins (g %)	7.6	6.2	5.3	—	5.2	—	—	—	5.8
Chlorides (mg %) ...	550	550	520	—	560	—	—	—	620
Bicarbonate (vol %)	27	46	67	—	58	—	—	—	56
Non-prot.N (mg %)	83	60	40	—	—	—	—	—	32
Sodium (mEq./l.) ...	136	132	141	—	152	—	—	—	—
Potassium (mEq./l.)	7.2	4.8	3.7	—	5.1	—	—	—	—
BSP (mg %)	0.6	0.4	—	0.9	1.0	0.6	1.0	0.4	0.1

Comment: a boy of 2 weeks whose mother was syphilitic had been on a penicillin medication and was clinically asymptomatic. After an onset of diarrhea he quickly recovered from the acute stage, but general recovery progressed slowly. The liver was enlarged in the course of the disease and simultaneously the BSP tests repeatedly differed from the normal, returning to it with the beginning of clinical improvement. The patient's reaction to vitamin K was not studied. He was discharged after 9 weeks' residence in hospital.

Fatal cases

Case 34. *No.* 1583/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.400 g. At the age of three weeks the patient began to vomit excessively and had diarrhea. He was admitted 3 days later, on April 26, 1949. The patient was thin, dehydrated and deeply unconscious. Superficial respiration, lungs: nil. Weight 2.600 g. Liver palpable for 2 fb. Diarrhea and vomiting ++. Alkali R 24 vol %. Plasma potassium 3.8 mEq./l. BSP retention 1.0 mg %. He died during the following night, in spite of every effort.

Autopsy: Hyperaemia leptomeningeum et cerebri. Stasis pulmonum. Metamorphosis adiposa hepatis. Gastroenteritis catarrhalis.

Comment: a boy aged 3 weeks who was admitted in agone, and died a few hours later. The BSP test was different from the normal. The liver revealed fatty changes.

Case 35. *No.* 3306/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 4.250 g. The patient fell ill at the orphanage, and there was an alarming loss of weight 700 g within one week. He was admitted on Sept. 30, 1949 in agone. Plasma proteins 5.7 g %, chlorides 590 mg %. Alkali R 36 vol %. BSP retention 2.6 mg %. In spite of therapy, the patient survived only for a few hours.

Autopsy: Gastroenteritis catarrhalis. Metamorphosis adiposa hepatis.

Comment: a boy aged 6 weeks fell ill with diarrhea at the orphanage and was admitted one week later in a fully unconscious state. He died within a few hours. The BSP test differed from the normal. The liver revealed fatty ehanges.

Case 36. *No.* 1280/49. *Gastroenteritis. Stenosis pylori hypertrophica.*

The birth weight was 2.800 g. At the age of 3 weeks the patient began to vomit and diarrhea set in. On admission, March 30, 1949, the weight was 2.600 g. The patient was listless and dehydrated. Lungs, nil. Liver palpable for 1 fb. Hb. 97 %, R.B.C. 4.25 mill., Hcr. 40. Plasma proteins 4.6 g %, chlorides 670 mg %, Alkali R 34 vol %, Non-prot. N 70 mg %.

2 / 4. she vomited profusely and was very restless. Liquor: 0. BSP retention 0.6 mg %.

7 / 4. she vomited intensely. Diarrhea ++. Rtg: Stenosis pylori hypertrophica. BSP retention 0.2 mg %.

11 / 4. the patient had a sudden turn for the worse and became listless. Her breathing was difficult, she was cyanotic and the temperature subnormal. Lungs, nil. Death ensued.

Autopsy: Stenosis hypertrophica pylori Bronchopeumoniae l. a. Stasis hepatis.

Comment: a girl aged 1 month had an onset of diarrhea and vomiting at the age of 3 weeks. In hospital she was found to be pylorostenotic and she died in 2 weeks after having contracted acute pneumonia in the ward. The BSP test was different from the normal at the beginning of treatment.

Case 37. *No.* 1547/49. *Gastroenteritis. Intoxicatio. Vitium cordis congenitum.*

The birth weight was 3.750 g. According to the parents, the development was normal, but the patient had been affected for about one month with mild diarrhea, cough and rhinitis. A physician had been consulted, who established a heart defect. On admission, April 23, 1949, the patient was pale and delicate, dehydrated and hollow-eyed. The weight was 6.500 g. The heart sounds were dull, and a rough systolic murmur was heard over the whole heart. The liver was palpable for 1 fb. The stools were yellow, half-firm, no vomiting. Hb. 80 %, R.B.C. 4.65 mill., Alkali R 40 vol %.

26 / 4. the weight was 6.300 g. The stools were fairly loose, the general condition was satisfactory. Rtg: Vitium cordis. BSP retention 0.3 mg %.

29 / 4. the weight was 6.000 g. Diarrhea and vomiting ++. General condition poor. Hb. 87 %, R.B.C. 4.90 mill., Hcr. 37, Plasma proteins 4.7 g %, chlorides 545 mg %, Alk. R 36 vol %. BSP retention 0.9 mg %.

30 / 4. the patient was very bad, listless and of a greyish pallor. T. 39.5°. Lungs, nil. Alk. R 36 vol %. BSP retention 1.4 mg %. She died during the night.

Autopsy: Oedema leptomeningeum. Hypertrophia ventriculi sinistri cordis. Ductus Botalli persistens. Metamorphosis adiposa hepatis. Stasis pulmonum. Gastroenteritis catarrhalis.

Comment: a girl of 7 months, who had been ill for one month with mild diarrhea and was found to have a congenital heart failure. During her residence in hospital there was at first no diarrhea, but the weight diminished daily, the baby began to vomit and the stools became loose. She died after 8 days in a toxic condition. The BSP test was normal on admission, but the retention increased as death approached. Autopsy revealed an open ductus Botalli and fatty changes in the liver.

Case 38. *No.* 1659/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.000 g. One week prior to admission the patient fell ill at the orphanage with fever, vomiting and diarrhea. On admission May 1, 1949, she was pale, dehydrated and unconscious. The stools were watery and green. Lungs, nil. The abdomen was tense, the liver not palpable. Next day the general condition was still poor. BSP retention 1.7 mg %.

5 / 5. the patient was listless and looked very ill. She vomited profusely, her stools were mixed with blood. BSP retention 1.5 mg %.

7 / 5. the condition was unchanged, there were petechiae on the skin. BSP retention 3.5 mg %.

1 0 / 5. Diarrhea and vomiting ++. The abdomen was distended. BSP retention 1.6 mg %. The patient died during the night.

Autopsy: Oedema pulmonum. Metamorphosis adiposa hepatis et renum. Gastroenteritis catarrhalis.

Weight and blood chemistry during disease

Date	2/5	5/5	7/5	10/5
Weight (gms)	4.400	4.400	4.450	4.500
Hemoglobin (%)	119	87	80	97
R.B.C. (mill.)	5.25	4.54	4.23	4.82
Hematocrit (%)	50	40	38	44
Proteins (g %)	4.6	4.5	5.0	4.8
Chlorides (mg %)	490	560	595	570
Bicarbonate (vol %).....	31	64	47	48
Non-prot.N (mg %)	41	—	—	45
Sodium (mEq./1.)	—	128	—	146
Potassium (mEq./1.).....	—	2.4	—	2.5
B S P (mg %)	1.7	1.5	3.5	1.6

Comment: a girl of 4 months who fell ill with acute diarrhea at the orphanage. She was unconscious on admission and died 9 days later. The plasma potassium was low. The BSP test departed several times from the normal. The reaction to vitamin K was slow. Autopsy revealed fatty changes in the liver.

Case 39. *No.* 1884/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.300 g. On May 10, 1949, the patient fell ill at the orphanage, vomited and was feverish. The loss in weight was 600 g. On admission, one week later, he was practically unconscious, dehydrated, of a greyish pallor and hollow-eyed. Cough and rhinitis +, lungs: nil. The abdomen was distended, the liver palpable for 1 fb. The vomit was streaked with blood. On the following day T. 38.5^0, the patient still seemed toxic and vomited ex-

cessively. The stools were watery, green and offensive, and they were mixed with blood. BSP retention 2.2 mg %.

2 0 / 5. T. 39.5°. The general condition was still poor, the vomiting intense. BSP retention 1.7 mg %.

2 2 / 5. temperature normal. The vomiting continued. The patient had nystagmus and convulsions. Plasma Ca 7.7 mg %. BSP retention 1.2 mg %.

2 5 / 5. the stools improved, but he continued to vomit. Convulsions occurred at times. The liver was palpable for 2 fb. BSP retention 1.3 mg %.

2 7 / 5. the patient was still in a very poor condition and vomited. The plasma Ca was 7.9 mg % in spite of therapy. BSP retention 1.5 mg %.

2 9 / 5. he had vomited 16 times within 24 hours. He was fully unconscious. BSP retention 2.4 mg %. He died during the night.

A u t o p s y : Oedema pulmonum. Metamorphosis adiposa hepatis. Degeneratio parenchymatosa renum. Gastroenteritis catarrhalis.

Weight and blood chemistry during disease

Date	19/5	22/5	25/5	28/5
Weight (gms)	5.300	5.100	4.800	5.000
Hemoglobin (%)	81	81	66	—
R.B.C. (mill.)	4.30	4.42	3.64	—
Hematocrit (%)	—	38	29	—
Proteins (g %)	6.1	5.2	6.0	5.2
Chlorides (mg %)	510	525	500	620
Bicarbonate (vol %).....	36	72	76	58
Non-prot.N (mg %)	36	—	33	—
Sodium (mEq./1.)	141	136	148	146
Potassium (mEq./1.).....	3.1	3.5	—	2.8
B S P (mg %)	2.2	1.2	2.1	2.4

C o m m e n t : a boy of 4 months with previously good health who had fallen ill at the orphanage with vomiting and diarrhea. During his residence in hospital he vomited profusely and became alkalotic. He repeatedly had convulsions. The plasma potassium and calcium were low. He died unconscious 10 days later. The BSP tests differed the whole time from the normal, and the retention grew as death approached. The reaction to vitamin K was negative. Autopsy revealed fatty changes in the liver.

C a s e 40. *No.* 1906/49. *Gastroenteritis. Intoxicatio. Eczema infantum.*

The birth weight was 2.800 g. The patient had had eczema from the beginning and measles at the age of 6 months. Because of eczema he was being treated at another hospital where he contracted diarrhea on May 9, 1949, and the weight fell with 1.200 g. On admission, May 20, 1949, the ge-

neral condition was poor, the patient was dehydrated and of a greyish pallor, and reacted slowly. Lungs, nil, moist eczema on the face. The vomit was mixed with blood, the stools were loose and revealed the growth of beta-hemolytic streptococci. The liver was not palpable. Next day BSP retention was 2.1 mg %.

2 2 / 5. the general condition was better. BSP retention 1.1 mg %.

2 5 / 5. Diarrhea and vomiting ++. BSP retention 1.2 mg %.

2 8 / 5. T. 40°. The patient coughed, rales were heard in the right lung. He vomited profusely. Plasma Ca 7.6 mg %, no convulsions. BSP retention 0.8 mg %.

2 9 / 5. he was very tired, feverish and continued to vomit. BSP retention 1.2 mg %. The patient died during the night.

A u t o p s y : Oedema et hyperaemia leptomeningeum. Oedema pulmonum et pneumonia l. dx. Metamorphosis adiposa hepatis. Gastroenteritis catarrhalis.

Weight and blood chemistry during disease

Date	21/5	23/5	25/5	28/5	30/5
Weight (gms)	6.200	6.100	6.300	5.800	6.000
Hemoglobin (%) ...	85	—	79	—	—
R.B.C. (mill.)	5.58	—	5.17	—	—
Proteins (g %)	5.0	5.3	5.3	4.7	4.7
Chlorides (mg %) ...	660	600	590	665	590
Bicarbonate (vol %)	32	45	72	53	39
Sodium (mEq./l.) ...	174	160	161	—	146
Potassium (mEq./l.)	1.6	1.8	—	—	1.5
B S P (mg %)	2.1	0.9	1.2	1.2	1.2

C o m m e n t: a boy aged 9 months who had been affected with eczema since his early life. While under treatment at another hospital, he fell ill with diarrhea and was transferred to us in a poor general condition. He contracted pneumonia during treatment and died 10 days later. The BSP tests were persistently different from the normal, and the reaction to vitamin K was slow. Plasma potassium and calcium were low. Autopsy revealed fatty changes in the liver.

C a s e 41. *No.* 1910/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.150 g. The patient had an onset of diarrhea at the age of 3 weeks. She fell ill again on May 7, 1949, and had been treated at another hospital. The weight loss was 1.200 g. On admission, May 20, 1949, she was in a poor general condition, thin, pale and dehydrated. The weight was 3.000 g. Lungs, nil. The stools were green and slimy, she vomited

profusely and sometimes brought up blood. The liver was palpable for 1 fb. On the following day she continued to vomit. Hb. 88 %, R.B.C. 4.22 mill., Hcr. 43. Plasma proteins 5.9 g %, chlorides 580 mg %, Alk. R 34 vol %, sodium 126 mEq./1, potassium 1.8 mEq./1. Blood-streaked stools. BSP retention 0.4 mg %.

2 3 / 5. there was no diarrhea but the patient continued to vomit. Alk. R 56 vol %. Plasma potassium 1.6 mEq./l. BSP retention 0.6 mg %. Convulsions occurred.

2 5 / 5. the patient was still tired but did not vomit anymore. Plasma potassium 1.8 mEq./1, calcium 6.3 mg %. She still had convulsions. BSP retention 0.6 mg %.

2 7 / 5. Death occurred while the condition remained unaltered.

A u t o p s y : Stasis pulmonum. Metamorphosis adiposa hepatis. Gastroenteritis catarrhalis.

C o m m e n t : a girl of 3 months who was being treated for diarrhea at another hospital. She was transferred to us in a typically postacidotic state and died 7 days later. The plasma potassium and calcium values were exceedingly low and the patient had convulsions. Potassium solutions were not given. The BSP test was only slightly different from the normal. The reaction to vitamin K was negative.

C a s e 42. *No.* 2098/49. *Gastroenteritis. Intoxicatio. Praematurus.*

The birth weight was 2.000 g. The patient fell ill at the orphanage 2 weeks before and lost 700 g. Diarrhea improved, but convulsions set in. On admission, June 7, 1949, he was fully unconscious, dehydrated and of a greyish pallor. Abundant petechiae were seen on the skin. Alk. R 16 vol %. Next day: Hb. 89 %, R.B.C. 5.01 mill., Hcr. 40, Plasma proteins 5.2 g %, chlorides 510 mg %, Alk. R 22 vol %, Non-prot. N 179 mg %. BSP retention 1.5 mg %.

1 0 / 6. he was clearly better, but the stools were green, loose and streaked with blood. Alk. R 56 vol %. BSP retention 0.8 mg %.

1 3 / 6. No diarrhea. Alk. R 52 vol %, potassium 2.4 mEq/1, calcium 8.0 mg %. BSP retention 1.4 mg %.

1 4 / 6. There was a rise in temperature, late in the evening it was 39^0. In the morning he became unconscious and had violent convulsions before he died.

A u t o p s y : Oedema pulmonum. Metamorphosis adiposa hepatis. Gastroenteritis catarrhalis.

C o m m e n t : a boy of 6 months who fell ill with diarrhea at the orphanage and was admitted 2 weeks later with a subnormal temperature, suffering from convulsions and acidotic. He seemed to recover, but a week later he ran a temperature, had convulsions and died. Plasma potassium and calcium were low. There was no reaction to vitamin K. During the whole time the BSP tests were different from the normal.

Case 43. *No.* 2306/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.450 g. Four days before admission the patient fell ill with vomiting and diarrhea, and suffered now and then from convulsions. On admission, June 28, 1949, the general condition was poor, the patient was thin, dehydrated and reacted slowly. The weight was 2.600 g. Lungs, nil; the abdomen was distended, the liver not palpable. Diarrhea ++. Hb. 117 %, R.B.C. 5.38 mill., Hcr. 56. Plasma proteins 6.3 mg %, chlorides 615 mg %, Alk. R 25 vol %. BSP retention 0.6 mg %.

30 / 6. T. 41°. Thorax rtg: 0. He vomited profusely and had convulsions. Alk. R 45 vol %, calcium 9 mg %. BSP retention 0.7 mg %.

4 / 7. the patient was still feverish and continued to vomit. The stools were mixed with blood. BSP retention 1.7 mg %.

7 / 7. the temperature fell, but the general condition was poor. Convulsions appeared at times. BSP retention 1.6 mg %.

10 / 7. subnormal temperature, the patient vomited intensely. Alk. R 81 vol %. BSP retention 1.7 mg %. He died during the night.

Autopsy was not performed.

Comment: a boy of 1 month who was admitted in a poor condition and died 12 days later. There was no reaction to vitamin K. The BSP retention increased as death approached.

Case 44. *No.* 428/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.600 g. The patient had been previously healthy and of normal development. He had suffered for two weeks with diarrhea, vomiting and fever. On admission, Jan. 14, 1949, he was dehydrated and hollow-eyed, of a greyish pallor and unconscious. T. 38°, lungs, nil. The abdomen was distended, the liver palpable for 1 fb. The vomit was mixed with blood, diarrhea ++. Acidosis cleared up two days later and the general condition improved. Diarrhea and vomiting ++.

21 / 1. he relapsed with diarrhea, after having been better meanwhile. BSP retention 0.1 mg %.

24 / 1. he was tired, listless, and did not eat well. There was blood in the stools and petechiae on the skin. The liver was palpable for 3 fb. BSP retention 0.3 mg %.

26 / 1. the patient was very sleepy and reacted slowly. The temperature swinging between 37—40°. He vomited profusely. No diarrhea. BSP retention 1.0 mg %.

29 / 1. The general condition was still poor. The skin symptoms increased. The liver filled the entire right iliac fossa. BSP retention 1.3 mg %.

2 / 2. he vomited intensely, the temperature fluctuated. Lungs, nil. The patient died during the night.

Autopsy: Oedema et hyperaemia leptomeningeum. Metamorphosis adiposa hepatis. Gastroenteritis catarrhalis.

Weight and blood chemistry during disease

Date	14/1	21/1	24/1	28/1	1/2
Weight (gms)	5.900	6.400	5.900	5.900	5.800
Hemoglobin (%)	90	93	—	56	60
R.B.C. (mill.)	4.66	5.14	—	—	3.31
Hematocrit (%)	43	44	—	—	26
Proteins (g %)	6.8	5.6	6.1	5.1	5.4
Chlorides (mg %) ...	620	630	640	610	640
Bicarbonate (vol %)	35	85	70	80	57
Non-prot.N (mg %)	91	27	—	22	—
B S P (mg %)	—	0.1	0.3	1.3	1.6

Comment: a boy aged 6 months with previously good health, who had been ill at home with diarrhea for 2 weeks. On admission he was in a poor condition and acidotic, but seemed to pick up at first. He died, however, 3 weeks later in a septic condition. The liver was strongly enlarged and the reaction to vitamin K negative. The BSP retention grew as death approached. Autopsy revealed a massive fatty liver.

Case 45. *No.* 1592/49. *Gastroenteritis. Intoxicatio. Praematurus.*

The birth weight was 2.150 g. The patient fell ill on April 21, 1949, with vomiting and diarrhea. On admission, 3 days later, his general condition was poor, he was thin, dehydrated and pale. Lungs, nil. Liver not palpable. Diarrhea ++.

28/4. the general condition was still poor. BSP retention 1.2 mg %.

30/4. the patient was of a greyish pallor, the abdomen tense. Stools and vomit were mixed with blood. BSP retention 0.7 mg %.

5/5. no diarrhea, the vomiting was less profuse. BSP retention 0.2 mg %.

11/5. the patient was still rather tired. The stools were mixed with blood. BSP retention 0.2 mg %.

18/5. he continued to vomit, was listless and atrophic. The stools were mixed with blood. Blood calcium 8.1 mg %. BSP retention 0.4 mg %.

21/5. the general condition was poor. BSP retention 0.3 mg %.

24/5. the condition was unchanged, the liver not palpable. BSP retention 0.1 mg %. The patient died during the night.

Autopsy: Hyperaemia leptomeningeum et cerebri. Stasis pulmonum et hepatis et renum. Gastroenteritis catarrhalis.

Comment: a premature infant aged 2 months who suffered from severe diarrhea and was admitted in a poor general condition and a state of atrophy. In spite of the treatment he was unable to pick up, but slowly

Weight and blood chemistry during disease

Date	28/4	30/4	5/5	11/5	18/5	24/5
Weight (gms)	3.000	3.000	2.900	3.000	2.700	2.400
Hemoglobin (%)	87	64	69	—	58	—
R.B.C. (mill.)	3.82	3.02	2.95	—	2.58	—
Hematocrit (%)	40	32	30	—	30	—
Proteins (g %)	5.3	5.2	4.8	5.7	5.5	5.2
Chlorides (mg %)	545	525	500	580	550	590
Bicarbonate (vol %).....	39	47	69	60	64	73
Non-prot.N (mg %).....	38	38	23	—	—	—
Sodium (mEq./l.)	—	159	144	153	131	139
Potassium (mEq./l.).....	—	3.5	3.9	3.3	3.6	3.7
B S P (mg %)	1.2	0.7	0.2	0.2	0.4	0.1

wasted away during one month. The plasma potassium was low throughout. The BSP test differed from the normal only at the beginning of treatment, but remained normal as death approached. During the later stage of the disease the reaction to vitamin K was clearly negative three times.

C a s e 46. *No.* 1892/49. *Gastroenteritis. Praematura.*

The birth weigt was 2.400 g. The patient had had fever, cough and diarrhea for a week. On admission, May 16, 1949, she was thin and dehydrated but fully conscious. Temperature subnormal, lungs, nil. Alk. R. 31 vol %. Diarrhea ++.

2 0 / 5. Alk. R. 47 vol %. BSP retention 0.8 mg %.

2 6 / 5. The weight was 2.200 g. The patient seemed alert. No diarrhea. BSP retention 0.4 mg %.

2 / 6. The patient was well. BSP retention 0.4 mg %.

9 / 6. BSP retention 0.4 mg %.

1 6 / 6. The weight was 2.600 g. She had begun to vomit again, and had mild diarrhea.

2 0 / 6. Diarrhea and vomiting ++. Alk. R 43 vol %. BSP retention 0.4 mg %.

2 5 / 6. the weight was 2.250 g. She was exceedingly tired and pale. The abdomen was distended. Lungs, nil. The patient died during the night. Autopsy was not performed.

C o m m e n t : a premature girl of 3 weeks who fell ill with diarrhea attended with fever and was admitted one week later. Her general condition was fairly good, and recovery progressed satisfactorily. The patient relapsed, however, and died after six weeks, probably of pneumonia. The BSP test differed from the normal only at the beginning of treatment.

Case 47. *No.* 2263/49. *Gastroenteritis.*

The birth weight was 2.950 g. The patient had been previously healthy, but fell ill in early June with diarrhea and vomiting, and was sent 2 weeks later to another hospital, from which she was transferred to us in a week. On admission, June 22, 1949, she was thin and dehydrated, as well as exceedingly, restless. Diarrhea ++. Liver palpable for 1 fb. BSP retention 0.7 mg %.

26/6. she was still very restless and whimpered continuously. Liquor: 0. The stools were loose, green and mixed with blood. BSP retention 1.0 mg %

30/6. she was pale and restless. The liver was palpable for 2 fb. BSP retention 1.2 mg %.

4/7. the patient was listless and the appetite still very poor. BSP retention 1.9 mg %.

7/7. she was tired and listless. The stools were slimy and mixed with blood. Liver palpable for 2 fb. BSP retention 2.4 mg %.

14/7. the appetite was better and the patient more lively. BSP retention 1.2 mg %.

20/7. liver palpable for 3 fb. BSP retention 1.4 mg %.

27/7. the patient was pale and tired. During these days she vomited profusely and was feverish. BSP retention 1.4 mg %.

3/8. the temperature persisted. Lung rtg: 0. She vomited excessively, the stools were mixed with blood. BSP retention 1.0 mg %.

14/8. Temperature normal. The general condition was still deteriorating. The liver filled the entire right iliac fossa. The stools were mixed with blood. BSP retention 0.8 mg %.

21/8. Her temperature had begun to rise again. The liver was unchanged. She vomited profusely and was greatly distressed. BSP retention 1.2 mg %. She died 2 days later.

Autopsy: Hyperaemia et oedema leptomeningeum et cerebri. Necrosis partialis lobi parietalis sinistri cerebri. Oedema pulmonum. Metamorphosis adiposa hepatis. Nephrosis. Atrophia.

Weight and blood chemistry during disease

Date	22/6	30/6	7/7	14/7	20/7	27/7	3/8	14/8	21/8
Weight (gms)	6.200	6.200	5.900	5.900	5.500	5.300	5.100	5.000	4.700
Hemoglobin (%)	77	—	70	77	69	73	98	—	140
R.B.C. (mill.)	4.00	—	3.81	4.11	3.76	4.10	4.97	—	7.00
Hematocrit (%)	35	—	33	36	—	34	—	—	56
Proteins (g %)	4.5	4.3	4.6	5.1	5.9	5.0	6.2	5.8	—
Chlorides (mg %) ...	525	565	590	565	480	590	620	590	—
Bicarbonate (vol %)	50	72	54	40	60	48	52	47	41
BSP (mg %)	0.7	1.2	2.4	1.2	1.4	1.4	1.0	0.8	1.2

Comment: a girl of 8 months who was at first under treatment at home, and then for one week at another hospital. On admission, she was in a typical postacidotic state and exceedingly restless, which suggested that her brain was affected. In spite of treatment, she became progressively worse and died after 9 weeks' residence in hospital in a state of cachexia. The liver was strongly enlarged and the reaction to vitamin K was repeatedly negative. The BSP tests differed the whole time from the normal. Autopsy revealed local necrosis of the parietal cerebral lobe and massive fatty liver.

Case 48. *No.* 2979/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 4.250 g. The patient had previously good health, and a normal development. She fell ill with fever, vomiting and diarrhea, and the condition was rapidly aggravated in 3 days. On admission, Sept. 4, 1949, she was dehydrated, of a greyish pallor and unconscious. T. 39°. She coughed; lungs, nil. The liver was palpable for 1 fb. Diarrhea ++.

11/9. she was still feverish and had convulsions at times. Blood calcium 8.3 mg %. Liver palpable for 3 fb. BSP retention 2.5 mg %.

16/9. Temperature normal. The patient was deeply unconscious, did not react or swallow. She had convulsions and gross edema. Rales were heard in both lungs. The liver was palpable for fb., the stools were mixed with blood. BSP retention 1.4 mg %.

23/9. the temperature began to rise again. The stools were mixed with blood. BSP retention 1.6 mg %.

29/9. the patient was unconscious and had convulsions. Blood calcium 8.8 mg %. Blood was still present in the stools. The liver filled the entire right iliac fossa and reached on the left to below the navel. BSP retention 1.8 mg %.

Weight and blood chemistry during disease

Date	5/9	11/9	16/9	23/9	29/9	2/10	5/10
Weight (gms)	5.850	6.100	6.300	6.000	5.600	5.500	5.300
Hemoglobin (%)	77	75	91	119	104	—	—
R.B.C. (mill.)	4.14	3.81	4.30	5.79	4.20	—	—
Hematocrit (%)	35	32	38	52	43	—	—
Proteins (g %)	6.0	5.3	4.6	5.4	4.3	4.1	3.9
Chlorides (mg %)	580	570	545	585	525	590	580
Bicarbonate (vol %)...	27	74	54	72	58	62	43
Non-prot.N (mg %) ...	24	33	33	37	37	—	—
Sodium (mEq./1.)	154	155	137	154	148	168	—
Potassium (mEq./1.)...	4.5	4.8	6.3	4.6	4.0	3.7	—
B S P (mg %)	—	2.5	1.4	1.6	1.8	1.6	1.8

5 / 1 0. The temperature had fallen. The patient was quite unconscious and had convulsions. BSP retention 1.8 mg %. She died during the following night.

A u t o p s y : Hyperaemia leptomeningeum. Pneumonia lobi superioris pulmonis dx. Metamorphosis adiposa hepatis. Nephrosis. Gastroenteritis catarrhalis.

C o m m e n t : a girl of 4 months who, on admission, was unconscious and in a poor condition. She died 5 weeks later, after having been unconscious for practically the whole time. She suffered continually from convulsions, and the blood calcium was low in spite of treatment. The liver was grossly enlarged and the reaction to vitamin K was clearly negative. The BSP tests differed from the normal for the entire duration of the disease. Autopsy revealed massive fatty liver and pneumonia.

C a s e 49. *No.* 3246/49. *Gastroenteritis. Intoxicatio. Stenosis duodeni congenita.*

The birth weight was 3.050 g. The patient had vomited ever since her birth. On Sept. 23, 1949, the stools became loose, and next day, on admission the patient was deeply unconscious, thin and dehydrated. Lungs, nil. Liver impalpable. Alk. R 29 vol %. Diarrhea ++.

2 6 / 9. The general condition was better but diarrhea continued. The vomit was of a greenish tint. Peristalsis was not visible in the abdominal wall Alk. R 45 vol %. BSP retention 0.6 mg %.

1 / 1 0. the weight was 2.650 g. Diarrhea was still severe. She had convulsions. Blood calcium 9.3 mg %. BSP retention 0.5 mg %.

1 0 / 1 0. the stools were somewhat better. The vomiting continued, at times of a greenish tint. Alk. R 56 vol %. BSP retention 0.8 mg %.

2 0 / 1 0. the weight was 2.600 g. No diarrhea, vomiting increased. Convulsions occurred at times. Blood calcium 9.1 mg %. Intestine rtg: Atresia partialis duodeni. BSP retention 0.2 mg %.

2 4 / 1 0. Laparotomy, duodeno-jejunostomy and enterostomy were performed.

2 5 / 1 0. Post-operative condition: the patient was very tired, vomited profusely, and died during the night. Autopsy was not performed.

C o m m e n t : a girl of 2 weeks who had vomited since birth, contracted diarrhea and was admitted in a poor condition. She made a good recovery from acidosis and diarrhea, but the vomiting continued, and the patient was found to be affected with congenital duodenal stenosis. She did not survive the operation. While diarrhea was in progress, the BSP test was different from the normal.

C a s e 50. No. 3396/49. *Gastroenteritis. Intoxicatio.*

The birth weight was 3.700 g. The patient was well developed and weighed 5.300 g before the onset. She had been suffering for a week with diarrhea

and vomiting. On admission, Oct. 7, 1949, she was pale and dehydrated, and reacted slowly to pinching. Lungs, nil. Liver impalpable. Diarrhea ++. BSP retention 0.5 mg %.

14/10. she was better, but her stools were still in a poor condition. The vomiting became more copious. BSP retention 0.4 mg %.

21/10. diarrhea and vomiting ++. BSP retention 0.7 mg %.

2/11. the patient was listless and her appetite poor, she vomited. The liver was palpable for 1 fb. BSP retention 1.0 mg %.

9/11. she was worse. The alkali reserve was exceedingly labile. BSP retention 1.2 mg %.

18/11. her condition continued to deteriorate. The liver was palpable for 2 fb. BSP retention 1.4 mg %.

24/11. the patient was still quite unconscious and died in the morning.

Autopsy: Hyperaemia leptomeningeum. Oedema pulmonum. Metamorphosis adiposa hepatis. Nephrosis. Atrophia.

Weight and blood chemistry during disease

Date	7/10	14/10	21/10	2/11	9/11	18/11	24/11
Weight (gms)	3.800	4.200	3.800	3.800	3.700	3.550	3.200
Hemoglobin (%)	77	102	104	97	113	75	89
R.B.C. (mill.)	3.34	4.10	4.72	4.50	4.73	3.21	4.32
Hematocrit (%)	34	42	47	43	46	33	36
Proteins (g%)	5.8	4.7	5.6	6.7	6.5	5.6	4.9
Chlorides (mg %)	515	610	525	570	590	650	590
Bicarbonate (vol %)...	42	43	69	29	49	38	29
Non-prot.N (mg %) ...	17	38	26	46	32	30	51
Sodium (mEq./l.)	143	142	147	149	149	136	148
Potassium (mEq./l.)...	5.6	5.0	4.8	3.2	3.4	3.4	2.3
BSP (mg %)	0.5	0.4	0.7	1.0	1.2	1.4	—

Comment: a girl of 3 months who was admitted after having been ill with diarrhea for a week at home and lost 1.500 g. On admission her general condition was fairly satisfactory, she had no acidosis. However, she did not recover normally, instead, she began to vomit profusely and gradually deteriorated in the course of 7 weeks. The liver became enlarged while the disease ran its course, and the BSP retention increased as death approached. Her reaction to vitamin K was not studied. Autopsy revealed massive fatty liver.

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